CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-722

Name: Ketorolac Tromethamine Injection USP, 15 mg/1 mL, 30 mg/1 mL, and 60 mg/2 mL, packaged in single-dose syringes

Sponsor: Apotex Corp.

Approval Date: July 27, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-722

CONTENTS

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-722

APPROVAL LETTER

ANDA 76-722

JUL 27 2004

Apotex Corp.
Attention: Marcy Macdonald
616 Heathrow Drive
Lincolnshire, IL 60069

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated April 11, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ketorolac Tromethamine Injection USP, 15mg/1 mL, 30mg/1 mL, and 60 mg/2 mL, packaged in single-dose syringes.

Reference is also made to your amendments dated December 23, 2003; and February 10, and March 17, 2004.

We note that the reference listed drug product (RLD) upon which you have based this application, Toradol® Injection of Roche Palo Alto LLC (Roche), is no longer being marketed in the United States. Thus, the agency has relocated Roche's Toradol® Injection to the Discontinued section of the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book". However, the agency has made the determination that Toradol® Injection was not withdrawn from sale for reasons of safety or effectiveness. This determination, which will be announced in the Federal Register, allows the agency to approve ANDAs for the discontinued drug product.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Ketorolac Tromethamine Injection USP, 15mg/1 mL, 30 mg/1 mL, and 60mg/2 mL, to be bioequivalent and, therefore, therapeutically equivalent to the current listed drug (Ketorolac Tromethamine Injection USP, 15 mg/1 mL, 30 mg/1 mL, and 60 mg/2 mL, respectively, of Bedford Laboratories).

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

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

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Robert Lumpkin for 1/27/2004

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

cc: ANDA 76-722
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-620/A.Yusef/ 7-15-04
HFD-623/A.Mueller/ 7/15/04
HFD-617/S.Eng/
HFD-613/J.Barlow/ 7/15/04
HFD-613/J.Grace/ 7/16/04
HFD-600/B.Pillari/ 7-15-04
HFD-600/N.Sweeney/

Robert West 1/27/2004

V:\FIRMSAM\Apotex\ltrs&rev\76722.AP.DOC
F/T by se

APPROVAL

7/20/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-722

APPROVED LABELING

Ketorolac Tromethamine Injection, USP

℞ ONLY

WARNING

Ketorolac tromethamine, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days in adults) management of moderately severe acute pain that requires analgesia at the opioid level. It is NOT indicated for minor or chronic painful conditions. Ketorolac tromethamine is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse events can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately. Increasing the dose of ketorolac tromethamine beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

Gastrointestinal Effects:

- Ketorolac tromethamine can cause peptic ulcers, gastrointestinal bleeding and/or perforation. Therefore, ketorolac tromethamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.

Renal Effects:

- Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion (see **WARNINGS**).

Risk of Bleeding:

- Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding (see **WARNINGS** and **PRECAUTIONS**)
- Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery and is CONTRAINDICATED intraoperatively when hemostasis is critical because of the increased risk of bleeding.

Hypersensitivity:

- Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock, have occurred and appropriate counteractive measures must be available when administering the first dose of Ketorolac Tromethamine Injection, USP (see **CONTRAINDICATIONS** and **WARNINGS**). Ketorolac tromethamine is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

Intrathecal or Epidural Administration:

- Ketorolac tromethamine is CONTRAINDICATED for intrathecal or epidural administration due to its alcohol content.

Labor, Delivery and Nursing:

- The use of ketorolac tromethamine in labor and delivery is CONTRAINDICATED because it may adversely affect fetal circulation and inhibit uterine contractions.
- The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates.

Concomitant Use with NSAIDs

- Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risk of inducing serious NSAID-related side effects.

DOSAGE AND ADMINISTRATION

Ketorolac Tromethamine Tablets:

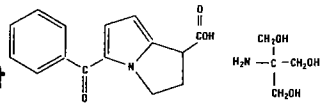
- Ketorolac Tromethamine Tablets are indicated only as continuation therapy to Ketorolac Tromethamine Injection USP, and the combined duration of use of Ketorolac Tromethamine Injection USP and Ketorolac Tromethamine Tablets is not to exceed 5 (five) days because of the increased risk of serious adverse events.
- The recommended total daily dose of Ketorolac Tromethamine Tablets (maximum 40 mg) is significantly lower than for Ketorolac Tromethamine Injection, (maximum 120 mg) (see **DOSAGE AND ADMINISTRATION**).

Special Populations:

- Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs) of body weight (see **DOSAGE AND ADMINISTRATION**) and for patients with moderately elevated serum creatinine (see **WARNINGS**). Doses of Ketorolac Tromethamine Injection, USP are not to exceed 60 mg (total dose per day) in these patients. Ketorolac Tromethamine Injection is indicated as a single dose therapy in pediatric patients (see **DOSAGE AND ADMINISTRATION**); not to exceed 30 mg for IM administration and 15 mg for IV administration.

DESCRIPTION

Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). The chemical name for ketorolac tromethamine is (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol(1:1), and the chemical structure is:



Ketorolac tromethamine is a racemic mixture of [-]S and [+]R ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. Ketorolac tromethamine has a pKa of 3.5 and an n-octanol/water partition coefficient of 0.26. The molecular weight of ketorolac tromethamine is 376.41. Its molecular formula is $C_{19}H_{24}N_2O_5$.

Ketorolac tromethamine is available for intravenous (IV) or intramuscular (IM) administration as: 15 mg in 1 mL (1.5%) and 30 mg in 1 mL (3%) in sterile solution, and in 60 mg in 2 mL (3%) of ketorolac tromethamine in sterile solution is available for IM administration only. The solutions contain 10% (w/v) alcohol, USP, and 6.68 mg, 4.35 mg and 8.70 mg, respectively, of sodium chloride in sterile water. The pH is adjusted with sodium hydroxide and/or hydrochloric acid. The sterile solutions are clear and slightly yellow in color.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity in animal models. Ketorolac tromethamine inhibits synthesis of prostaglandins and may be considered a peripherally acting analgesic. The biological activity of ketorolac tromethamine is associated with the S-form. Ketorolac tromethamine possesses no sedative or anxiolytic properties.

The peak analgesic effect of ketorolac tromethamine occurred within 2 to 3 hours and is not statistically significantly different over the recommended dosage range of ketorolac tromethamine. The greatest difference between large and small doses of ketorolac tromethamine by either route was in the duration of analgesia.

Pharmacokinetics:

Ketorolac tromethamine is a racemic mixture of [-]S- and [+]R-enantiomeric forms, with the S-form having analgesic activity.

Comparison of IV, IM and Oral Pharmacokinetics: The pharmacokinetics of ketorolac tromethamine, following IV, IM and oral doses of ketorolac tromethamine, are compared in Table 1. In adults, the extent of bioavailability following administration of the ORAL and IM forms of ketorolac tromethamine was equal to that following an IV bolus.

TABLE I
Table of Approximately Average Pharmacokinetic Parameters (Mean ± SD)
Following Oral, Intramuscular and Intravenous Doses of Ketorolac Tromethamine

Pharmacokinetic Parameters (units)	Oral*	Intramuscular†			Intravenous Bolus ‡	
	10 mg	15 mg	30 mg	60 mg	15 mg	30 mg
Bioavailability (extent)				100%		
T_{max}[1] (min)	44 ± 34	33 ± 21§	44 ± 29	33 ± 21§	1.1 ± 0.7§	2.9 ± 1.8
C_{max}[2] (µg/mL) [single-dose]	0.87 ± 0.22	1.14 ± 0.32§	2.42 ± 0.68	4.55 ± 1.27§	2.47 ± 0.51§	4.65 ± 0.96
C_{max} (µg/mL) [steady state qid]	1.05 ± 0.26§	1.56 ± 0.44§	3.11 ± 0.87§	N/A‖	3.09 ± 1.17§	6.85 ± 2.61
C_{min}[3] (µg/mL) [steady state qid]	0.29 ± 0.07§	0.47 ± 0.13§	0.93 ± 0.26§	N/A	0.61 ± 0.21§	1.04 ± 0.35
C_{avg}[4] (µg/mL) [steady state qid]	0.59 ± 0.20§	0.94 ± 0.29§	1.88 ± 0.59§	N/A	1.09 ± 0.30§	2.17 ± 0.59
Vβ[5] (L/kg)	----------0.175 ± 0.039----------				0.210 ± 0.044	

% Dose metabolized = <50
% Dose excreted in urine = 91
%Dose excreted in feces = 6
%Plasma protein binding = 99

[1]Time-to-peak plasma concentration
[2]Peak plasma concentration
[3]Through plasma concentration
[4]Average plasma concentration
[5]Volume of distribution

* Derived from PO pharmacokinetic studies in 77 normal fasted volunteers
† Derived from IM pharmacokinetic studies in 54 normal volunteers
‡ Derived from IV pharmacokinetic studies in 24 normal volunteers
§ Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed C_{max} and T_{max} data
‖ Not applicable because 60 mg is only recommended as a single dose

Linear Kinetics: In adults, following administration of single ORAL, IM or IV doses of ketorolac tromethamine in the recommended dosage ranges, the clearance of the racemate does not change. This implies that the pharmacokinetics of ketorolac tromethamine in humans, following single or multiple IM, IV or recommended oral doses of ketorolac tromethamine, are linear. At the higher recommended doses, there is a proportional increase in the concentrations of free and bound racemate.

Distribution: The mean apparent volume (V(beta)) of ketorolac tromethamine following complete distribution was approximately 13 liters. This parameter was determined from single-dose data. The ketorolac tromethamine racemate has been shown to be highly protein bound (99%). Nevertheless, even plasma concentrations as high as 10 µg/mL will only occupy approximately 5% of the albumin binding sites. Thus, the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations.

Ketorolac tromethamine is excreted in human milk (see **PRECAUTIONS: Lactation and Nursing**).

Metabolism: Ketorolac tromethamine is largely metabolized in the liver. The metabolic products are hydroxylated and conjugated forms of the parent drug. The products of metabolism, and some unchanged drug, are excreted in the urine.

Excretion: The principal route of elimination of ketorolac and its metabolites is renal. About 92% of a given dose is found in the urine, approximately 40% as metabolites and 60% as unchanged ketorolac. Approximately 6% of a dose is excreted in the feces. A single-dose study with 10 mg ketorolac tromethamine (n=9) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer and that the clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S- form in humans. The clearance of the racemate in normal subjects, elderly individuals and in hepatically and renally impaired patients is outlined in Table 2. (see **CLINICAL PHARMACOLOGY:** *Kinetics in Special Populations*).

Table 2
The Influence of Age, Liver and Kidney Function, on the Clearance and Terminal Half-life of Ketorolac Tromethamine (IM[1] and ORAL[2]) in Adult Populations

Type of Subjects	Total Clearance (in L/h/kg)[3]		Terminal Half-life (in hours)	
	IM Mean (range)	ORAL Mean (range)	IM Mean (range)	ORAL Mean (range)
Normal Subjects IM (n=54) mean age=32, range=18-60 Oral (n=77) mean age=32, range=20-60	0.023 (0.010-0.046)	0.025 (0.013-0.050)	5.3 (3.5-9.2)	5.3 (2.4-9.0)
Healthy Elderly Subjects IM (n=13), Oral (n=12) mean age=72, range=65-78	0.019 (0.013-0.034)	0.024 (0.018-0.034)	7.0 (4.7-8.6)	6.1 (4.3-7.6)
Patients with Hepatic Dysfunction IM and Oral (n=7) mean age=51, range=43-64	0.029 (0.013-0.066)	0.033 (0.019-0.051)	5.4 (2.2-6.9)	4.5 (1.6-7.6)
Patients with Renal Impairment IM (n=25), Oral (n=9) serum creatinine=1.9-5.0 mg/dL, mean age (IM)=54, range=35-71 mean age (Oral)=57, range=39-70	0.015 (0.005-0.043)	0.016 (0.007-0.052)	10.3 (5.9-19.2)	10.8 (3.4-18.9)
Renal Dialysis Patients IM and Oral (n=9) mean age=40, range=27-63	0.016 (0.003-0.036)	—	13.6 (8.0-39.1)	—

[1]Estimated from 30 mg single IM doses of ketorolac tromethamine
[2]Estimated from 10 mg single oral doses of ketorolac tromethamine
[3]Liters/hour/kilogram

IV Administration: In normal adult subjects (n=37), the total clearance of 30 mg IV-administered ketorolac tromethamine was 0.030 (0.017-0.051) L/h/kg. The terminal half-life was 5.6 (4.0-7.9) hours. (See *Kinetics in Special Populations* for use of Ketorolac Tromethamine Injection, USP in pediatric patients).

The half-life of ketorolac tromethamine S-enantiomer was approximately 2.5 hours (SD ± 0.4) compared with 5 hours (SD ± 1.7) for the R-enantiomer. In other studies, the half-life for the racemate has been reported to lie within the range of 5 to 6 hours.

Accumulation: Ketorolac tromethamine administered as an IV bolus every 6 hours for 5 days to healthy subjects (n= 13), showed no significant difference in C_{max} on Day 1 and Day 5. Trough levels averaged 0.29 μg/mL (SD ± 0.13) on Day 1 and 0.55 μg/mL (SD ± 0.23) on Day 6. Steady state was approached after the fourth dose.

Accumulation of ketorolac tromethamine has not been studied in special populations (geriatric, pediatric, renal failure patients or hepatic disease patients).

Kinetics in Special Populations: Geriatric Patients: Based on single-dose data only, the half-life of the ketorolac tromethamine racemate increased from 5 to 7 hours in the elderly (65 to 78 years) compared with young healthy volunteers (24 to 35 years) (see Table 2). There was little difference in the C_{max} for the two groups (elderly, 2.52 μg/mL ± 0.77; young, 2.99 μg/mL ± 1.03) (see **PRECAUTIONS – Geriatric Use**).

Pediatric Patients: Following a single intravenous bolus dose of 0.5 mg/kg in 10 children 4 to 8 years old, the half-life was 6 hours (range: 3.5 to 10 h), the average clearance was 0.042 L/hr/kg and the Vd was 0.26 L/kg (range: 0.19 to 0.44 L/kg). In a second study, following a single intravenous dose of 0.6 mg/kg in 24 children 3 to 18 years old C_{max} was 4.3 ± 2.6 mcg/mL, T_{max} was 10.25 ± 1.15 minutes, half-life was 3.8 ± 2.6 hours, Cl was 0.0678 L/hr/kg and Vd was 0.25 L/kg. The volume of distribution and clearance of ketorolac in pediatric patients was twice that observed in adult subjects (see **Tables 1** and **2**). There are no pharmacokinetic data available for ketorolac tromethamine administration by the IM route in pediatric patients.

Renal Insufficiency: Based on single-dose data only, the mean half-life of ketorolac tromethamine in renally impaired patients is between 6 and 19 hours and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total ketorolac tromethamine clearance in the elderly and populations with renal impairment ($r = 0.5$).

In patients with renal disease, the AUC_∞ of each enantiomer increased by approximately 100% compared with healthy volunteers. The volume of distribution doubles for the S-enantiomer and increases by 1/5th for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction.

The AUC_∞ -ratio of the ketorolac tromethamine enantiomers in healthy subjects and patients remained similar, indicating there was no selective excretion of either enantiomer in patients compared to healthy subjects (see **WARNINGS - Renal Effects** and **Table 2**).

Hepatic Insufficiency: There was no significant difference in estimates of half-life, AUC_∞ and C_{max} in 7 patients with liver disease compared to healthy volunteers (see **PRECAUTIONS** - *Hepatic Effects* and **Table 2**).

Race: Pharmacokinetic differences due to race have not been identified.

Clinical Studies:

Adult Patients: The analgesic efficacy of intramuscularly, intravenously and orally administered ketorolac tromethamine was investigated in two postoperative pain models: general surgery (orthopedic, gynecologic and abdominal) and oral surgery (removal of impacted third molars). The studies were double-blind, single- and multiple-dose, parallel trial designs in patients with moderate to severe pain at baseline. Ketorolac tromethamine injection was compared as follows: IM to meperidine or morphine administered intramuscularly and IV to morphine administered either directly IV or through a PCA (Patient-Controlled Analgesia) pump.

Short-Term Use (up to 5 days) Studies: In adults, the comparisons of intramuscular administration during the first hour, the onset of analgesic action was similar for ketorolac tromethamine and the narcotics, but the duration of analgesia was longer with ketorolac tromethamine than with the opioid comparators meperidine or morphine.

In a multi-dose, postoperative (general surgery) double-blind trial of Ketorolac 30 mg IM versus morphine 6 and 12 mg IM, each drug given on an as needed basis for up to 5 days, the overall analgesic effect of Ketorolac 30 mg IM was between that of morphine 6 and 12 mg. The majority of patients treated with either ketorolac tromethamine or morphine were dosed for up to 3 days; a small percentage of patients received 5 days of dosing.

In clinical settings where preoperative morphine was allowed, Ketorolac 30 mg IV, given once or twice as needed, provided analgesia comparable to morphine 4 mg IV once or twice as needed.

There was relatively limited experience with 5 consecutive days of Ketorolac IV use in controlled clinical trials, as most patients were given the drug for 3 days or less. The adverse events seen with IV-administered ketorolac tromethamine were similar to those observed with IM-administered ketorolac tromethamine, as would be expected based on the similar pharmacokinetics and bioequivalence (AUC, clearance, plasma half-life) of IV and IM routes of ketorolac tromethamine administration.

Pediatric Patients: The analgesic efficacy of single doses of Ketorolac Tromethamine Injection, had been demonstrated by showing a decrease in the need for supplemental narcotic in pediatric patients receiving ketorolac as compared to placebo. See discussion of these results under *Clinical Studies With Concomitant Use of Opioids* below.

Clinical Studies with Concomitant Use of Opioids: Adult Patients: Clinical studies in postoperative pain management have demonstrated that Ketorolac Tromethamine Injection, when used in combination with opioids, significantly reduced opioid consumption. This combination may be useful in the subpopulation of patients especially prone to opioid-related complications. Ketorolac tromethamine and narcotics should not be administered in the same syringe.

In a postoperative study, where all patients received morphine by a PCA device, patients treated with Ketorolac intravenously as fixed intermittent boluses (e.g., 30 mg initial dose followed by 15 mg q3h), required significantly less morphine (26%) than the placebo group. Analgesia was significantly superior, at various postdosing pain assessment times, in the patients receiving Ketorolac intravenously plus PCA morphine as compared to patients receiving PCA-administered morphine alone.

Pediatric Patients: Ketorolac Tromethamine Intramuscular Injection reduced the need for supplemental opioid (fentanyl) when a 1 mg/kg dose was administered immediately following tonsillectomy compared to saline controls (see **WARNINGS**: *Hemorrhage*). In another study, when a single bolus dose of 0.9 mg/kg of Ketorolac Tromethamine Intravenous Injection was given to pediatric patients ages 5 to 12 years, compared to saline, a reduction in supplemental opioid was needed following various surgical procedures. In a third study less supplemental morphine was needed in pediatric patients ages 8 to 16 years, who received a 0.8 mg/kg IV injection of ketorolac tromethamine in conjunction with morphine following orthopedic surgical procedures, compared to morphine alone. In a study in pediatric patients ages 3 to 12 years, Ketorolac Tromethamine Intravenous Injection demonstrated a slower onset of analgesia, but a longer duration of action compared to morphine. There is limited data available to support the use of multiple doses of Ketorolac Tromethamine Injection in pediatric patients.

Postmarketing Surveillance Study: A large postmarketing observational, non-randomized study, involving approximately 10,000 patients receiving ketorolac tromethamine, demonstrated that the risk of clinically serious gastrointestinal (GI) bleeding was dose-dependent (see **Tables 3A** and **3B**). This was particularly true in elderly patients who received an average daily dose greater than 60 mg/day of ketorolac tromethamine (**Table 3A**).

Table 3
Incidence of Clinically Serious GI Bleeding as Related to Age, Total Daily Dose, and History of GI Perforation, Ulcer, Bleeding (PUB) after up to 5 Days of Treatment with Ketorolac Tromethamine Injection, USP

A. Adult Patients without History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine Injection, USP			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	0.4%	0.4%	0.9%	4.6%
≥65 years of age	1.2%	2.8%	2.2%	7.7%

B. Adult Patients with History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine Injection, USP			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	2.1%	4.6%	7.8%	15.4%
≥65 years of age	4.7%	3.7%	2.8%	25.0%

INDICATIONS AND USAGE

Adult Patients: Ketorolac tromethamine injection is indicated for the short-term (≤5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with Ketorolac Tromethamine Injection and Ketorolac Tromethamine Tablets are to be used only as continuation treatment, if necessary. Combined use of Ketorolac Tromethamine Injection and Ketorolac Tromethamine Tablets is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses (see **WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION** and **ADVERSE REACTIONS**). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

Pediatric Patients: The safety and effectiveness of single doses of Ketorolac Tromethamine Injection have been established in pediatric patients between the ages of 2 and 16 years. Ketorolac tromethamine, as a single injectable dose, has been shown to be effective in the management of moderately severe acute pain that requires analgesia at the opioid level, usually in the postoperative setting. There is limited data available to support the use of mutiple doses of ketorolac tromethamine in pediatric patients. Safety and effectiveness have not been established in pediatric patients below the age of 2 years. Use of ketorolac tromethamine in pediatric patients is supported by the evidence from adequate and well-controlled studies of ketorolac tromethamine in adults with additional pharmacokinetic, efficacy and safety data on its use in pediatric patients available in the published literature (see **CLINICAL PHARMACOLOGY:** *Clinical Studies,* **WARNINGS**, and **PRECAUTIONS**).

Ketorolac Tromethamine Injection has been used concomitantly with morphine and meperidine and has shown an opioid-sparing effect. For breakthrough pain, it is recommended to supplement the lower end of the Ketorolac Tromethamine Injection dosage range with low doses of narcotics prn, unless otherwise contraindicated. Ketorolac Tromethamine Injection and narcotics should not be administered in the same syringe (see **DOSAGE AND ADMINISTRATION - Pharmaceutical Information for Ketorolac Tromethamine Injection, USP**).

CONTRAINDICATIONS (see also BOXED WARNING)

- Ketorolac tromethamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.
- Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment or in patients at risk for renal failure due to volume depletion (see **WARNINGS** for correction of volume depletion).
- Ketorolac tromethamine is CONTRAINDICATED in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.
- The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates.
- Ketorolac tromethamine is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine, or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).
- Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery and is CONTRAINDICATED intra-operatively when hemostasis is critical because of the increased risk of bleeding.
- Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding (see **WARNINGS** and **PRECAUTIONS**).
- Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risks of inducing serious NSAID-related adverse events.
- Ketorolac Tromethamine Injection, USP is CONTRAINDICATED for neuraxial (epidural or intrathecal) administration due to its alcohol content.
- The concomitant use of ketorolac tromethamine and probenecid is CONTRAINDICATED.

WARNINGS (see also BOXED WARNING)

The combined use of Ketorolac Tromethamine Injection and Ketorolac Tromethamine Tablets is not to exceed 5 (five) days in adults. Only single doses of Ketorolac Tromethamine Injection are recommended for use in pediatric patients.

The most serious risks associated with ketorolac tromethamine are:

Gastrointestinal (GI) Effects
Risk of Gastrointestinal Ulcerations, Bleeding and Perforation:
Ketorolac tromethamine is CONTRAINDICATED in patients with previously documented peptic ulcers and/or GI bleeding. Serious gastrointestinal toxicity, such as bleeding, ulceration and perforation, can occur at any time, with or without warning symptoms, in patients treated with ketorolac tromethamine. Studies to date with NSAIDs have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Postmarketing experience with parenterally administered ketorolac tromethamine suggests that there may be a greater risk of gastrointestinal ulcerations, bleeding and perforation in the elderly.

The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, ketorolac tromethamine. In a non-randomized, in-hospital postmarketing surveillance study comparing parenteral ketorolac tromethamine to parenteral opioids, higher rates of clinically serious GI bleeding were seen in patients <65 years of age who received an average total daily dose of more than 90 mg of Ketorolac

Tromethamine Injection, USP per day (see **CLINICAL PHARMACOLOGY** - *Postmarketing Surveillance Study*).

The same study showed that elderly (≥65 years of age) and debilitated patients are more susceptible to gastrointestinal complications. A history of peptic ulcer disease was revealed as another risk factor that increases the possibility of developing serious gastrointestinal complications during ketorolac tromethamine therapy (see **Tables 3A** and **3B**).

Impaired Renal Function:
Ketorolac tromethamine should be used with caution in patients with impaired renal function or a history of kidney disease because it is a potent inhibitor of prostaglandin synthesis. Renal toxicity with ketorolac tromethamine has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of ketorolac tromethamine may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate acute renal failure. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of ketorolac tromethamine therapy is usually followed by recovery to the pretreatment state.

Renal Effects:
Ketorolac tromethamine and its metabolites are eliminated primarily by the kidneys, which, in patients with reduced creatinine clearance, will result in diminished clearance of the drug (see **CLINICAL PHARMACOLOGY**). Therefore, ketorolac tromethamine should be used with caution in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**) and such patients should be followed closely. With the use of ketorolac tromethamine, there have been reports of acute renal failure, nephritis and nephrotic syndrome.

Because patients with underlying renal insufficiency are at increased risk of developing acute renal failure, the risks and benefits should be assessed prior to giving ketorolac tromethamine to these patients. Hence, in patients with moderately elevated serum creatinine, it is recommended that the daily dose of Ketorolac Tromethamine Injection, USP be reduced by half, not to exceed 60 mg/day. **KETOROLAC TROMETHAMINE is CONTRAINDICATED in patients with serum creatinine concentrations indicating advanced renal impairment (see CONTRAINDICATIONS).**

Hypovolemia should be corrected before treatment with ketorolac tromethamine is initiated.

Fluid Retention and Edema:
Fluid retention, edema, retention of NaCl, oliguria, elevations of serum urea nitrogen and creatinine have been reported in clinical trials with ketorolac tromethamine. Therefore, ketorolac tromethamine should be used only very cautiously in patients with cardiac decompensation, hypertension or similar conditions.

Pregnancy: In late pregnancy, as with other NSAIDs, ketorolac tromethamine should be avoided because it may cause premature closure of the ductus arteriosus.

Hemorrhage:
Because prostaglandins play an important role in hemostasis and NSAIDs affect platelet aggregation as well, use of ketorolac tromethamine in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. Patients on therapeutic doses of anticoagulants (eg, heparin or dicumarol derivatives) have an increased risk of bleeding complications if given ketorolac tromethamine concurrently; therefore, physicians should administer such concomitant therapy only extremely cautiously. The concurrent use of ketorolac tromethamine and prophylactic low-dose heparin (2500 to 5000 units q12h), warfarin and dextrans have not been studied extensively, but may also be associated with an increased risk of bleeding. Until data from such studies are available, physicians should carefully weigh the benefits against the risks and use such concomitant therapy in these patients only extremely cautiously. In patients who receive anticoagulants for any reason, there is an increased risk of intramuscular hematoma formation from administered ketorolac intramuscularly (see **PRECAUTIONS - Drug Interactions**). Patients receiving therapy that affects hemostasis should be monitored closely.

In postmarketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association with the preoperative use of Ketorolac Tromethamine Injection. Therefore, preoperative use of ketorolac tromethamine should be avoided and postoperative use be undertaken with caution when hemostasis is critical (see **WARNINGS** and **PRECAUTIONS**).

Pediatrics and Tonsillectomy: Physicians should consider the increased risk of bleeding before deciding to administer ketorolac tromethamine in patients following tonsillectomy. Ketorolac Tromethamine Injection is not recommended for use in pediatric patients below the age of 2 years. In a retrospective analysis of patients having undergone tonsillectomy with or without adenoidectomy, the risk of bleeding was 10.1% in patients administered Ketorolac Tromethamine Injection compared to 2.2% in those receiving opioids. The postoperative hemorrhage rate in patients 12 years and younger was 6.5% and 3.3% with and without Ketorolac Tromethamine Injection, USP, respectively. In a prospective study of ketorolac tromethamine in pediatric patients (ages 3 to 9 years) undergoing tonsillectomy with or without adenoidectomy, the overall incidence of bleeding was similar between the patients receiving ketorolac tromethamine and morphine (16.3% versus 17%, respectively). However, during the first 24 hours after surgery, a higher incidence of bleeding was observed in the Ketorolac Tromethamine Injection group (14.3%) versus the morphine group (4.2%).

Anaphylactoid Reactions:
Anaphylactoid reactions may occur in patients without a known previous exposure or hypersensitivity to aspirin, ketorolac tromethamine or other NSAIDs, or in individuals with a history of angioedema, bronchospastic reactivity (e.g., asthma) and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

PRECAUTIONS

General:
Hepatic Effects: Ketorolac tromethamine should be used with caution in patients with impaired hepatic function or a history of liver disease. Treatment with ketorolac tromethamine may cause elevations of liver enzymes, and, in patients with pre-existing liver dysfunction, it may lead to the development of a more severe hepatic reaction. The administration of ketorolac tromethamine should be discontinued in patients in whom an abnormal liver test has occurred as a result of ketorolac tromethamine therapy.

Hematologic Effects: Ketorolac tromethamine inhibits platelet aggregation and may prolong bleeding time; therefore, it is contraindicated as a preoperative medication, and caution should be used when hemostasis is critical. Unlike aspirin, the inhibition of platelet function by ketorolac tromethamine disappears within 24 to 48 hours after the drug is discontinued. Ketorolac tromethamine does not appear to affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). In controlled clinical studies, where ketorolac tromethamine was administered intramuscularly or intravenously postoperatively, the incidence of clinically significant postoperative bleeding was 0.4% for ketorolac tromethamine compared to 0.2% in the control groups receiving narcotic analgesics.

Information for Patients:
Ketorolac tromethamine is a potent NSAID and may cause serious side effects such as gastrointestinal bleeding or kidney failure, which may result in hospitalization and even fatal outcome.

Physicians, when prescribing ketorolac tromethamine, should inform their patients or their guardians of the potential risks of ketorolac tromethamine treatment (see **BOXED WARNING, WARNINGS, PRECAUTIONS** and **ADVERSE REACTIONS** sections). *Advise patients not to give Ketorolac Tromethamine Tablets to other family members and to discard any unused drug.*

Remember that the total duration of ketorolac tromethamine therapy is not to exceed 5 (five) days in adults or single dose in pediatric patients ages 2 to 16 years.

Drug Interactions:
Ketorolac is highly bound to human plasma protein (mean 99.2%).

Warfarin, Digoxin, Salicylate and Heparin
The *in vitro* binding of ***warfarin*** to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control vs 99.3%) when ketorolac plasma concentrations reach 5 to 10 μg/mL. Ketorolac does not alter digoxin protein binding. *In vitro* studies indicate that, at therapeutic concentrations of ***salicylate*** (300 μg/mL), the binding of ketorolac was reduced from approximately 99.2% to 97.5%, representing a potential two-fold increase in unbound ketorolac plasma levels. Therapeutic concentrations of ***digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin*** and ***tolbutamide*** did not alter ketorolac tromethamine protein binding.

In a study involving 12 adult volunteers, Ketorolac Tromethamine Tablets were coadministered with a single dose of 25 mg ***warfarin***, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, Ketorolac Tromethamine Injection, USP was given with two doses of 5000 U of ***heparin*** to 11 healthy volunteers, resulting in a mean template bleeding time of 6.4 minutes (3.2 to 11.4 min) compared to a mean of 6.0 minutes (3.4 to 7.5 min) for heparin alone and 5.1 minutes (3.5 to 8.5 min) for placebo. Although these results do not indicate a significant interaction between ketorolac tromethamine and warfarin or heparin, the administration of ketorolac tromethamine to patients taking anticoagulants should be done extremely cautiously, and patients should be closely monitored (see **WARNINGS** and **PRECAUTIONS**).

Furosemide
Ketorolac Tromethamine Injection reduced the diuretic response to ***furosemide*** in normovolemic healthy subjects by approximately 20% (mean sodium and urinary output decreased 17%).

Probenecid
Concomitant administration of Ketorolac Tromethamine Tablets and ***probenecid*** resulted in decreased clearance of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately threefold from 5.4 to 17.8 μg/h/mL) and terminal half-life increased approximately twofold from 6.6 to 15.1 hours. Therefore, concomitant use of ketorolac tromethamine and probenecid is contraindicated.

Lithium
Inhibition of renal ***lithium*** clearance, leading to an increase in plasma lithium concentration, has been reported with some prostaglandin synthesis inhibiting drugs. The effect of ketorolac tromethamine on plasma lithium has not been studied, but cases of increased lithium plasma levels during ketorolac tromethamine therapy have been reported.

Methotrexate
Concomitant administration of ***methotrexate*** and some NSAIDs has been reported to reduce the clearance of methotrexate, enhancing the toxicity of methotrexate. The effect of ketorolac tromethamine on methotrexate clearance has not been studied.

Non-depolarizing Muscle Relaxants
In postmarketing experience there have been reports of a possible interaction between Ketorolac Tromethamine Injection, USP and ***non-depolarizing muscle relaxants*** that resulted in apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been formally studied.

ACE Inhibitors
Concomitant use of ***ACE inhibitors*** may increase the risk of renal impairment, particularly in volume depleted patients.

Antiepileptic Drugs
Sporadic cases of seizures have been reported during concomitant use of ketorolac tromethamine and ***antiepileptic drugs*** (phenytoin, carbamazepine).

Psychoactive Drugs
Hallucinations have been reported when ketorolac tromethamine was used in patients taking ***psychoactive drugs*** (fluoxetine, thiothixene, alprazolam).

Morphine
Ketorolac Tromethamine Injection has been administered concurrently with ***morphine*** in several clinical trials of postoperative pain without evidence of adverse interactions. Do not mix ketorolac tromethamine and morphine in the same syringe.

There is no evidence in animal or human studies that ketorolac tromethamine induces or inhibits hepatic enzymes capable of metabolizing itself or other drugs.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
An 18-month study in mice with oral doses of ketorolac tromethamine at 2 mg/kg/day (0.9 times the human systemic exposure at the recommended IM or IV dose of 30 mg qid, based on area-under-the-plasma-concentration curve [AUC]), and a 24-month study in rats at 5 mg/kg/day (0.5 times the human AUC) showed no evidence of tumorigenicity.

Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac tromethamine did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 µg/mL and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac tromethamine, respectively.

Pregnancy:
Pregnancy Category C: Reproduction studies have been performed during organogenesis using daily oral doses of ketorolac tromethamine at 3.6 mg/kg (0.37 times the human AUC) in rabbits and at 10 mg/kg (1.0 times the human AUC) in rats. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg (0.14 times the human AUC), administered after gestation Day 17, caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies of ketorolac tromethamine in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery:
The use of ketorolac tromethamine is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage (see **CONTRAINDICATIONS**).

Lactation and Nursing:
After a single administration of 10 mg Ketorolac Tromethamine Tablets to humans, the maximum milk concentration observed was 7.3 ng/mL, and the maximum milk-to-plasma ratio was 0.037. After 1 day of dosing (qid), the maximum milk concentration was 7.9 ng/mL, and the maximum milk-to-plasma ratio was 0.025. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers is CONTRAINDICATED.

Pediatric Use:
Safety and effectiveness of single doses of Ketorolac Tromethamine Injection have been established in pediatric patients between the ages of 2 and 16 years. Ketorolac Tromethamine Injection has been shown to be effective in the management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Safety and efficacy in pediatric patients below the age of 2 have not been established. Therefore, Ketorolac Tromethamine Injection is not recommended in pediatric patients below the age of 2. The risk of bleeding was greater in those patients administered Ketorolac Tromethamine Injection following tonsillectomy. Physicians should consider the increased risk of bleeding before deciding to administer Ketorolac Tromethamine Injection in patients following tonsillectomy (see **WARNINGS:** *Hemorrhage and Pediatrics and Tonsillectomy*).

The risks identified in the adult population with Ketorolac Tromethamine Injection use also apply to pediatric patients. Therefore, consult the **CONTRAINDICATIONS, WARNING, PRECAUTIONS,** and **ADVERSE REACTIONS** sections when prescribing Ketorolac Tromethamine Injection to pediatric patients.

Geriatric Use (≥65 years of age):
Because ketorolac tromethamine may be cleared more slowly by the elderly (see **CLINICAL PHARMACOLOGY**) who are also more sensitive to the adverse effects of NSAIDs (see **WARNINGS - Renal Effects**), extra caution and reduced dosages (see **DOSAGE AND ADMINISTRATION**) must be used when treating the elderly with ketorolac tromethamine injection. The lower end of the ketorolac tromethamine injection dosage range is recommended for patients over 65 years of age, and total daily dose is not to exceed 60 mg. The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, ketorolac tromethamine.

ADVERSE REACTIONS

Adverse reaction rates increase with higher doses of ketorolac tromethamine. Practitioners should be alert for the severe complications of treatment with ketorolac tromethamine, such as GI ulceration, bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions and liver failure (see **BOXED WARNING, WARNINGS, PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). These NSAID-related complications can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately.

The Adverse Reactions Listed Below Were Reported In Clinical Trials As Probably Related To Ketorolac Tromethamine:

- **Incidence Greater Than 1 %**
  Percentage of incidence in parentheses for those events reported in 3% or more patients.
  Body as a Whole: edema (4%)
  Cardiovascular: hypertension
  Dermatologic: pruritus, rash
  Gastrointestinal: nausea (12%), dyspepsia (12%), gastrointestinal pain (13%), diarrhea (7%), constipation, flatulence, gastrointestinal fullness, vomiting, stomatitis
  Hemic and Lymphatic: purpura
  Nervous System: headache (17%), drowsiness (6%), dizziness (7%), sweating
  Injection-site pain was reported by 2% of patients in multidose studies.
- **Incidence 1 % or Less**
  Body as a Whole: weight gain, fever, infections, asthenia
  Cardiovascular: palpitation, palfor, syncope
  Dermatologic: urticaria
  Gastrointestinal: gastritis, rectal bleeding, eructation, anorexia, increased appetite
  Hemic and Lymphatic: epistaxis, anemia, eosinophilia
  Nervous System: tremors, abnormal dreams, hallucinations, euphoria, extrapyramidal symptoms, vertigo, paresthesia, depression, insomnia, nervousness, excessive thirst, dry mouth, abnormal thinking, inability to concentrate, hyperkinesis, stupor
  Respiratory: dyspnea, pulmonary edema, rhinitis, cough
  Special Senses: abnormal taste, abnormal vision, blurred vision, tinnitus, hearing loss
  Urogenital: hematuria, proteinuria, oliguria, urinary retention, polyuria, increased urinary frequency

The Following Adverse Events Were Reported From Postmarketing Experience:

Body as a Whole: hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, tongue edema (see **BOXED WARNING, WARNINGS**), angioedema, myalgia
Cardiovascular: hypotension, flushing
Dermatologic: Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculopapular rash, urticaria
Gastrointestinal: peptic ulceration, GI hemorrhage, GI perforation (see **BOXED WARNING, WARNINGS**), melena, acute pancreatitis, hematemesis, esophagitis
Hemic and Lymphatic: post operative wound hemorrhage, rarely requiring blood transfusion (see **BOXED WARNING, WARNINGS** and **PRECAUTIONS**), thrombocytopenia, leukopenia
Hepatic: hepatitis, liver failure, cholestatic jaundice
Nervous System: convulsions, psychosis, aseptic meningitis
Respiratory: asthma, bronchospasm
Urogenital: acute renal failure (see **BOXED WARNING, WARNINGS**), flank pain with or without hematuria and/or azotemia, interstitial nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome

OVERDOSAGE

Symptoms following acute NSAIDs overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactiod reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following a NSAIDs overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 g to 100 g in adults, 1g/kg to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large oral overdose (5 to 10 times the usual dose).

In controlled overdosage, daily doses of 360 mg of Ketorolac Tromethamine Injection given for 5 days (three times the highest recommended dose), caused abdominal pain and peptic ulcers which healed after discontinuation of dosing. Metabolic acidosis has been reported following discontinuation of dosing. Metabolic acidosis has been reported following intentional overdosage.

Single overdoses of ketorolac tromethamine have been variously associated with abdominal pain, nausea, vomiting, hyperventilation, peptic ulcers and/or erosive gastritis and renal dysfunction which have resolved after discontinuation of dosing. Dialysis does not significantly clear ketorolac tromethamine from the blood stream.

DOSAGE AND ADMINISTRATION

IN ADULTS THE COMBINED DURATION OF USE OF KETOROLAC TROMETHAMINE INJECTION, USP AND KETOROLAC TROMETHAMINE TABLETS IS NOT TO EXCEED FIVE (5) DAYS. IN ADULTS THE USE OF KETOROLAC TROMETHAMINE TABLETS IS ONLY INDICATED AS CONTINUATION THERAPY TO KETOROLAC TROMETHAMINE INJECTION, USP.

Ketorolac Tromethamine Injection USP:
Adult Patients: Ketorolac Tromethamine Injection, USP may be used as a single, or multiple dose, on a regular or prn schedule for the management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Hypovolemia should be corrected prior to the administration of ketorolac tromethamine (see **WARNINGS - Renal Effects**). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

When administering ketorolac tromethamine injection, USP the IV bolus must be given over no less than 15 seconds. The IM administration should be given slowly and deeply into the muscle. The analgesic effect begins in ~30 minutes with maximum effect in 1 to 2 hours after dosing IV or IM. Duration of analgesic effect is usually 4 to 6 hours.

Single-Dose Treatment: The following regimen should be limited to single administration use only:

Adult Patients:
IM Dosing:
- Patients <65 years of age: One dose of 60 mg.
- Patients ≥ 65 years of age, renally impaired and/or less than 50 kg (110 lbs.) of body weight: One dose of 30 mg.

IV Dosing:
- Patients <65 years of age: One dose of 30 mg.

- Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs.) of body weight: One dose of 15 mg.

Pediatric Patients (2 to 16 years of age): The pediatric population should receive only a single dose of Ketorolac Tromethamine Injection, USP, as follows:

IM Dosing:
One dose of 1 mg/kg up to a maximum of 30 mg.

IV Dosing:
One dose of 0.5 mg/kg up to a maximum of 15 mg.

Multiple Dose Treatment (IV or IM) in Adults:
- Patients <65 years of age: The recommended dose is 30 mg Ketorolac Tromethamine Injection, USP every 6 hours. The maximum daily dose should not exceed 120 mg.
- For Patients ≥65 years of age, renally impaired patients (see **WARNINGS**) and patients less than 50 kg (110 lbs.): The recommended dose is 15 mg Ketorolac Tromethamine Injection every 6 hours. The maximum daily dose for these populations should not exceed 60 mg.

For breakthrough pain do not increase the dose or the frequency of ketorolac tromethamine. Consideration should be given to supplementing these regimens with low doses of opioids prn unless otherwise contraindicated.

Pharmaceutical Information for Ketorolac Tromethamine Injection:
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Ketorolac Tromethamine Injection, USP should not be mixed in a small volume (eg, in a syringe) with morphine sulfate, meperidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride; this will result in precipitation of ketorolac from solution.

Shortening the recommended dosing intervals may result in increased frequency and severity of adverse reactions.

In adults, the maximum combined duration of use (parenteral and oral ketorolac tromethamine) is limited to 5 days.

HOW SUPPLIED
Ketorolac Tromethamine Injection, USP is available as follows:

For IV/IM Single-Dose Use:
15 mg: 15 mg/mL, 1 mL pre-filled syringe
30 mg: 30 mg/mL, 1 mL pre-filled syringe

For IM Single-Dose Use:
60 mg: 30 mg/mL, 2 mL pre-filled syringe

Store at 20° to 25°C (68° to 77°F) [See USP controlled room temperature].

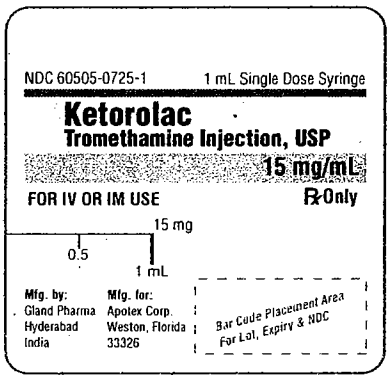
PROTECT FROM LIGHT.

Manufactured by:
Gland Pharma
Hyderabad
500 043 India

Revised: November 2003

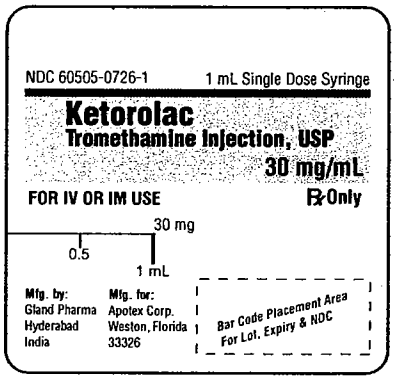
APPROVED

JUL 27 2004



ENLARGED TO 120%
BY FOI STAFF

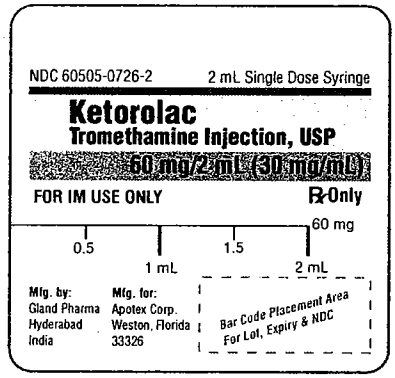
APPROVED



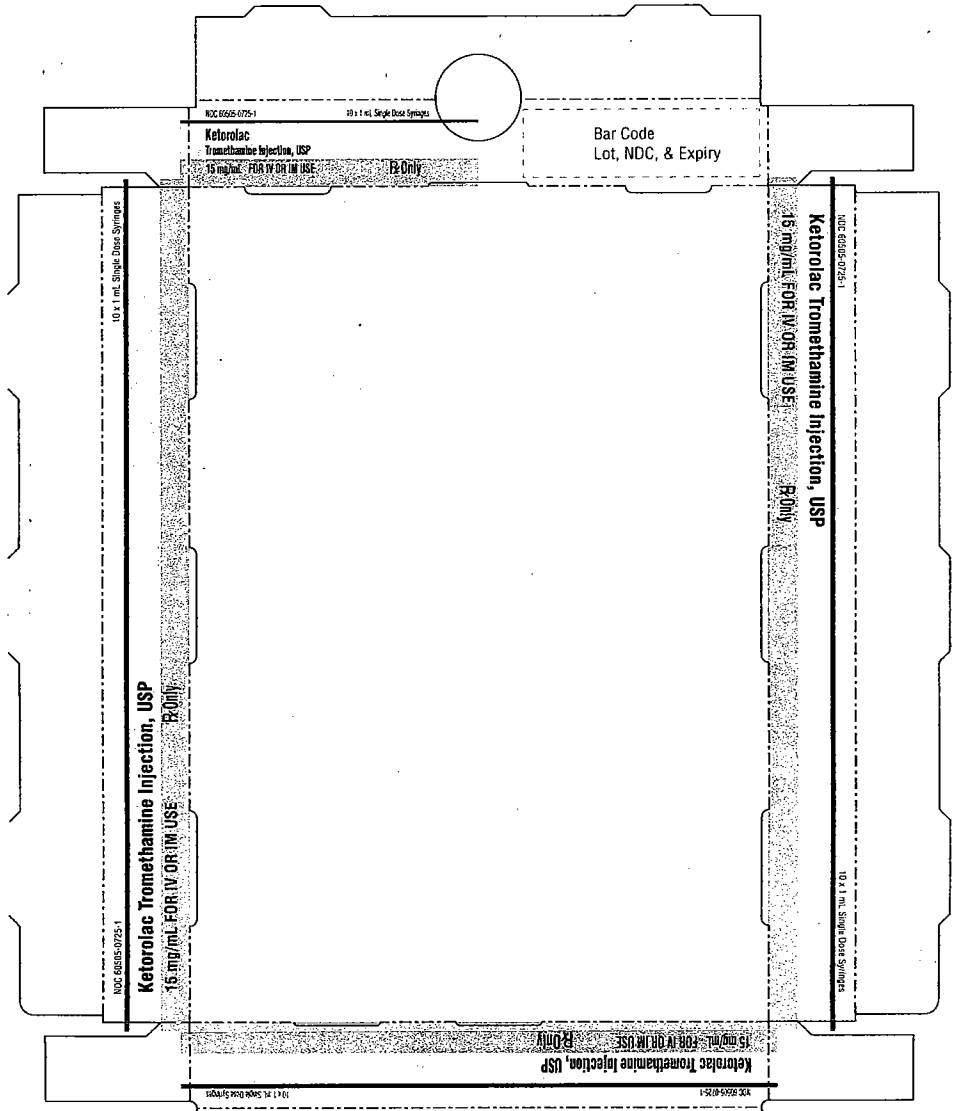
ENLARGED TO 120%
BY FOI STAFF

APPROVED

JUL 27 2004



ENLARGED TO 120%
BY FOI STAFF



NDC 60505-0725-1 10 x 1 mL Single Dose Syringes

Ketorolac
Tromethamine Injection, USP

15 mg/mL

FOR IV OR IM USE

℞Only

Usual Dosage: See package insert.

Each mL contains: 15 mg ketorolac tromethamine, USP, 10% (w/v) alcohol, USP, 6.68 mg sodium chloride, USP, Water for Injection, USP and sodium hydroxide, NF or hydrochloric acid, NF for pH adjustment.

Store at 20°-25°C (68°-77°F)
(See USP controlled room temperature).

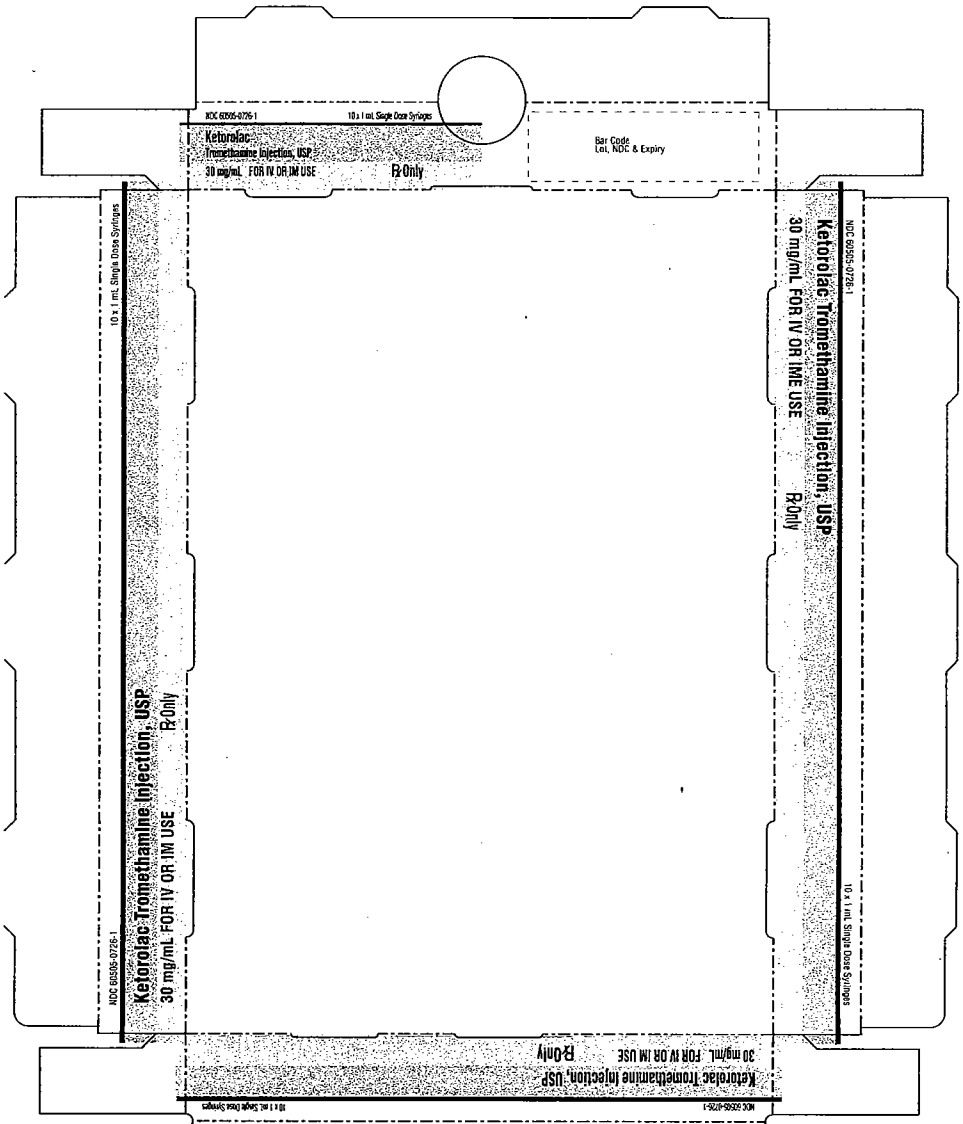
PROTECT FROM LIGHT
RETAIN IN CARTON UNTIL TIME OF USE

Mfg. by: Gland Pharma, Hyderabad, India
Mfg. for: Apotex Corp., Weston, FL 33326

APOTEX CORP.

APPROVED
JUL 27 2004

REDUCED TO 64%
BY FDI STAFF



NDC 60505-0726-1 10 x 1 mL Single Dose Syringes

Ketorolac
Tromethamine Injection, USP
30 mg/mL

FOR IV OR IM USE

℞Only

Usual Dosage: See package insert.

Each mL contains: 30 mg ketorolac tromethamine, USP, 10% (w/v) alcohol, USP, 4.35 mg sodium chloride, USP, Water for Injection, USP and sodium hydroxide, NF or hydrochloric acid, NF for pH adjustment.

Store at 20°-25°C (68°-77°F)
(See USP controlled room temperature).

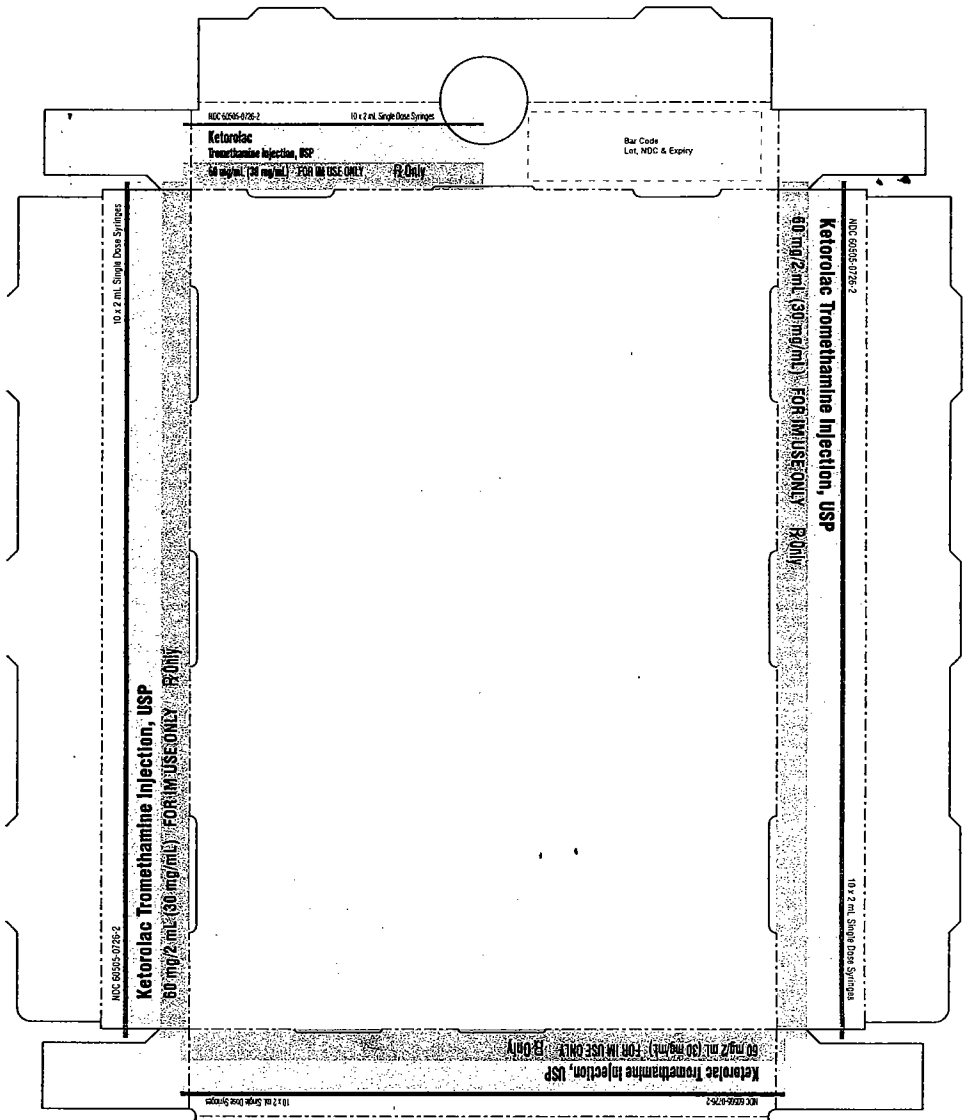
PROTECT FROM LIGHT
RETAIN IN CARTON UNTIL TIME OF USE

Mfg. by: Gland Pharma, Hyderabad, India
Mfg. for: Apotex Corp., Weston, FL 33326

APOTEX CORP.

APPROVED
JUL 27 2004

REDUCED TO 64%
BY FDA STAFF



NDC 60505-0726-2 10 x 2 mL Single Dose Syringes

Ketorolac
Tromethamine Injection, USP
60 mg/2mL (30 mg/mL)

FOR IM USE ONLY

Rx Only

Usual Dosage: See package insert.

Each mL contains: 30 mg ketorolac tromethamine, USP, 10% (w/v) alcohol, USP, 4.35 mg sodium chloride, USP, Water for Injection, USP and sodium hydroxide, NF or hydrochloric acid, NF for pH adjustment.

Store at 20°-25°C (68°-77°F)
(See USP controlled room temperature).

PROTECT FROM LIGHT
RETAIN IN CARTON UNTIL TIME OF USE

Mfg. by: Gland Pharma, Hyderabad, India
Mfg. for: Apotex Corp., Weston, FL 33326

APOTEX CORP.

APPROVED
JUL 27 2004

REDUCED TO 64%
BY FDI STAFF

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-722

LABELING REVIEW(S)

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

ANDA Number:	76-722
Date of Submission:	April 11, 2003
Applicant's Name:	Apotex Corp.
Established Name:	Ketorolac Tromethamine Injection USP, 15 mg/mL, 30 mg/mL and 60 mg/2mL

Labeling Deficiencies:

1. **CONTAINER – 1mL and 2 mL pre-filled syringes**
   Satisfactory in **draft** as of the April 11, 2003 submission

2. **CARTON – 10's**
   Satisfactory in **draft** as of the April 11, 2003 submission

3. **PACKAGE INSERT**
   Attached you will find mocked-up package insert labeling. Revise accordingly.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

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

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

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

Attached: Copy of mocked-up package insert labeling

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.	x		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.			x
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x		
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x

Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	x		
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? [Not recommended for pediatric use].		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? [See FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them? [See FTR]	x		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? [See FTR].	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. [Same as the RLD].		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T and date study acceptable) [pending]			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. [See FTR].			

FOR THE RECORD:

1. MODEL:
   a. Insert - Toradol injection/oral by Syntex [NDA 19-645/19-698]; approved October 11, 2001
   b. Container - Toradol by Snytex; approved October 11, 2001
   c. Also used was the labeling for ANDA 74-801 & 74-802 (Ketorolac Tromethamine Injection, Syringe & Vial) from Abbott.

2. PATENT and EXCLUSIVITY

Patent Data – NDA 19-645

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	***None***	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-645

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. PACKAGING: Apotex utilizes a different delivery system, therefore, it carved out info pertaining to the use of a Tubex.

   RLD -
   FOR IV/IM USE:
   15 mg: 15 mg/mL, 1 mL tubex-box of 10
   30 mg: 30 mg/mL, 1 mL tubex-box of 10
   FOR **IM** USE **ONLY:**
   60 mg: 30 mg/mL, 2 mL tubex-box of 1 & 10

   ANDA-
   15 mg: syringe 15 mg/mL, 1 mL x 10's
   30 mg: syringe 30 mg/mL, 1 mL x 10's
   60 mg: syringe 30 mg/mL, 2 mL x 10's (for IM use ONLY)

4. The expression of the alcohol % is accurate. (30 mg/mL)(See page 1993 in volume B. 1.5) Calculated 11.6%. 11.67% for 15 mg/mL (See pg 1836 in vol 1.5 red jacket)
   Does chemistry concur?

5. The firm has expressed the alcohol amount in w/v% rather than v/v%. According to section 502(e) of the Act and 21 CFR 201.10(d)(2) alcohol amount should be expressed in terms of percent volume (v/v%) of absolute alcohol rather than w/v%. However, the RLD's labeling also expressed in w/v%. **We will not ask the firm to revise.**

6. INACTIVES INGREDIENTS:
   The inactive ingredients listed in the DESCRIPTION section appear to be consistent with the firm's Composition statement [Vol.B 1.1, p.245].

7. STORAGE recommendations:
   USP- Preserve in single-dose containers, preferably of Type I glass, at controlled room temperature, protected from light.

   RLD- Store bottles at controlled room temperature, 15 to 30C (59 to 86F) with protection from light.

   ANDA-Store at controlled room temperature, 15-30C (59-86F). (See USP) PROTECT FROM LIGHT.
   Retain in carton until time of use.
   NOTE: THE SENTENCE, "RETAIN IN CARTON UNTIL TIME OF USE" IS NOT IN THE RLD LABELING. HOWEVER, THIS STATEMENT IS ACCEPTABLE AND WE WILL REQUEST OTHER GENERIC FIRMS TO INCLUDE THIS STATEMENT.

8. CONTAINER:
   Glass Barrels – 2.25 mL USP Type I. [Vol. B 1.3 pg. 981]

9. This product will be manufactured in Hyderabad, India for Apotex Corp.

The following is from the review done on ANDA 74-801 & 74-802 (Ketorolac Tromethamine Injection form Abbott).

Chan Park and Charlie Hoppes have determined (during review for ANDA ——— & 74-993, ketorolac tromethamine injection from ———) to include the text ——— and the subsection ——— under DOSAGE AND ADMINISTRATION section considering the regimen of this particular drug involves both parenteral and oral dosage forms as continuation therapy. However, the subsection ——— has been modified to reflect the exclusivity issue for Abbotts applications.
The information on oral ketorolac tromethamine is also to be retained under the DOSAGE AND ADMINISTRATION section in the BOXED WARNING at the beginning of the insert. Please note that in a previous review for ketorolac tromethamine tablets (ANDA 74-761 by Mylan), it has been decided that this

text be retained as well.

After review of the 5/19/97 package insert by Jerry Phillips, it was decided that the firm must again revise the insert (most importantly) because:

- **It was decided that information regarding specific dosing of the tablets in the DOSAGE AND**
- **ADMINISTRATION section is not necessary for an insert for the parenteral route of administration. [i.e.,** The text ——— and the subsection ———.]

Date of Review: 7/21/03 **Date of Submission: April 11, 2003**)

Reviewer: J Barlow **Date:** 7/24/03

Team Leader: J Grace **Date:** 7/30/2003

---

cc: ANDA 76-722
HFD-613/Jbarlow/JGrace/ (no cc:)
V:\FIRMSAM\Apotex\ltrs&rev\76722na1.l.doc
Review

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY

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

ANDA Number: 76-722
Date of Submission: February 10, 2004
Applicant's Name: Apotex Corp.
Established Name: Ketorolac Tromethamine Injection USP, 15 mg/mL, 30 mg/mL and 60 mg/2mL

APPROVAL SUMMARY

1. **Do you have 12 Final Printed Labels and Labeling?** Yes

2. **CONTAINER – 1mL and 2 mL pre-filled syringes**
   Satisfactory in **final print** as of the February 10, 2004 submission

2. **CARTON – 10's**
   Satisfactory in **final print** as of the February 10, 2004 submission

3. **PACKAGE INSERT**
   Satisfactory in **final print** as of the February 10, 2004 submission

4. **Revisions needed post-approval:** None

5. **Patent Data – NDA 19-698**

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	***None***	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-698

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Toradol® (Injection)
NDA Number: N 19-698
NDA Drug Name: Toradol® (Injection)
NDA Firm: Syntex Laboratories, Inc. Labs; N 19-698
Date of Approval of NDA Insert and supplement: October 11, 2001; NDA 19-698/S-016
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug.
Basis of Approval for the Carton Labeling: Most recently approved labeling of the reference listed drug.
OTHER COMMENTS: Note that AR was for NDA 19-698/ ——— was accepted ——— , the same info for NDA 19-645/S-011 approved October 11, 2001. Also note that new labeling found approvable (AE) ——— , may hold up approval for this application.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.	x		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			

PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.			x
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x		
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	x		
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? [Not recommended for pediatric use].		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x

Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? [See FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them? [See FTR]	x		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? [See FTR].	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. [Same as the RLD].		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T □ and date study acceptable) [pending]			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. [See FTR].			

FOR THE RECORD:

1. MODEL:
   a. Insert - Toradol injection/oral by Syntex
      [NDA 19-645/19-698]; approved October 11, 2001
   b. Container - Toradol by Snytex; approved October 11, 2001
   c. Also used was the labeling for ANDA 74-801 & 74-802 (Ketorolac Tromethamine Injection, Syringe & Vial) from Abbott.

2. PATENT and EXCLUSIVITY

Patent Data – NDA 19-645

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	***None***	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-645

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. PACKAGING: Apotex utilizes a different delivery system, therefore, it carved out info pertaining to the use of a Tubex.

RLD -
FOR IV/IM USE:
15 mg: 15 mg/mL, 1 mL tubex-box of 10
30 mg: 30 mg/mL, 1 mL tubex-box of 10
FOR **IM** USE **ONLY:**
60 mg: 30 mg/mL, 2 mL tubex-box of 1 & 10

ANDA-
15 mg: syringe 15 mg/mL, 1 mL x 10's
30 mg: syringe 30 mg/mL, 1 mL x 10's
60 mg: syringe 30 mg/mL, 2 mL x 10's (for IM use ONLY)

4. The expression of the alcohol % is accurate. (30 mg/mL)(See page 1993 in volume B. 1.5) Calculated 11.6%. 11.67% for 15 mg/mL (See pg 1836 in vol 1.5 red jacket)
   Does chemistry concur?

5. The firm has expressed the alcohol amount in w/v% rather than v/v%. According to section 502(e) of the Act and 21 CFR 201.10(d)(2) alcohol amount should be expressed in terms of percent volume

(v/v%) of absolute alcohol rather than w/v%. However, the RLD's labeling also expressed in w/v%. **We will not ask the firm to revise.**

6. INACTIVES INGREDIENTS:
   The inactive ingredients listed in the DESCRIPTION section appear to be consistent with the firm's Composition statement [Vol.B 1.1, p.245].

7. STORAGE recommendations:
   USP- Preserve in single-dose containers, preferably of Type I glass, at controlled room temperature, protected from light.

   RLD- Store bottles at controlled room temperature, 15 to 30C (59 to 86F) with protection from light.

   ANDA-Store at 20-25C (68-77F). (See USP controlled room temperature) PROTECT FROM LIGHT. Retain in carton until time of use.
   NOTE: THE SENTENCE, "RETAIN IN CARTON UNTIL TIME OF USE" IS NOT IN THE RLD LABELING. HOWEVER, THIS STATEMENT IS ACCEPTABLE AND WE WILL REQUEST OTHER GENERIC FIRMS TO INCLUDE THIS STATEMENT.

8. CONTAINER:
   Glass Barrels – 2.25 mL USP Type I. [Vol. B 1.3 pg. 981]

9. This product will be manufactured in Hyderabad, India for Apotex Corp.

The following is from the review done on ANDA 74-801 & 74-802 (Ketorolac Tromethamine Injection form Abbott).

Chan Park and Charlie Hoppes have determined (during review for ANDA ——— & 74-993, ketorolac tromethamine injection from ———) to include the text ——— and the subsection ——— under DOSAGE AND ADMINISTRATION section considering the regimen of this particular drug involves both parenteral and oral dosage forms as continuation therapy. However, the subsection ——— has been modified to reflect the exclusivity issue for Abbotts applications.
The information on oral ketorolac tromethamine is also to be retained under the DOSAGE AND ADMINISTRATION section in the BOXED WARNING at the beginning of the insert. Please note that in a previous review for ketorolac tromethamine tablets (ANDA 74-761 by Mylan), it has been decided that this text be retained as well.

After review of the 5/19/97 package insert by Jerry Phillips, it was decided that the firm must again revise the insert (most importantly) because:

- **It was decided that information regarding specific dosing of the tablets in the DOSAGE AND**
- **ADMINISTRATION section is not necessary for an insert for the parenteral route of administration. [i.e.,** The text ——— and the subsection ——— **]**

Date of Review: 2/27/04 **Date of Submission: 2/10/04**)

Reviewer: J Barlow **Date:** 3/1/04

Team Leader: J Grace **Date:** 3/2/04

---

cc: ANDA 76-722
HFD-613/Jbarlow/JGrace/ (no cc:)
V:\FIRMSAM\Apotex\ltrs&rev\76722ap.s.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-722

CHEMISTRY REVIEW(S)

#1

ANDA 76-722

Ketorolac Tromethamine Injection USP, 15 mg/mL and 30 mg/mL - Syringe

Apotex Corporation

Yusuf Amin
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-722

2. REVIEW #: 1

3. REVIEW DATE: 15 JUL 2003

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	11-APR-2003
Amendment	22-MAY-2003
FDA acknowledgement letter	03-JUN-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	11-APR-2003
Amendment	22-MAY-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Corporation
Address:	616 Heathrow Drive Lincolnshire, IL 60069
Representative:	Marcy Macdonald
Telephone:	(847) 279 7740

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ketorolac Tromethamine

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: Under section 505(j)(1) of FFD &CA.
Toradol Injection, 15 mg/mL and 30 mg/mL, the subject of NDA 19-698 held by Roche Palo.

The firm certifies that to the best of its knowledge, all patents related to Toradol Injection, 15 mg/mL and 30 mg/mL, held by Roche Palo have expired. The firm also certifies that in its opinion and to the best of its knowledge, there is no market exclusivity currently in effect for the listed drug, Toradol Injection, 15 mg/mL and 30 mg/mL.

10. PHARMACOL. CATEGORY: NSAID (Non Steroidal Anti-Inflammatory Drug)

11. DOSAGE FORM: Parenteral Solution for Administration by IV/IM Injection (Single-dose Syringe Unpreserved)

12. STRENGTH/POTENCY: 15 mg/mL and 30mg/mL

13. ROUTE OF ADMINISTRATION: IV/IM Injection

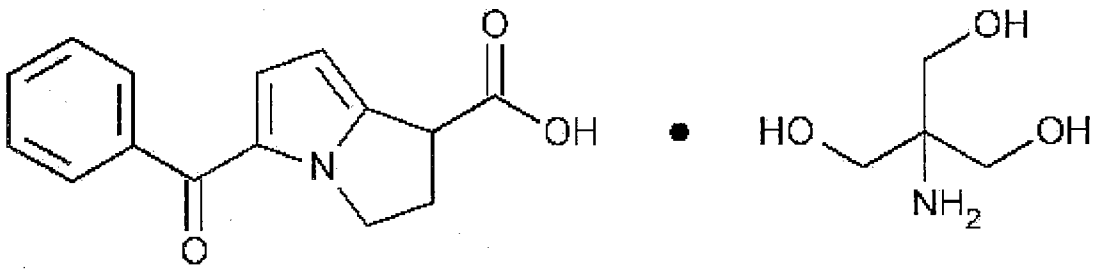
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

_____SPOTS product – Form Completed

_X_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Ketorolac Tromethamine
$C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$ 376.40
1H-Pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, (±)-, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).
(±)-5-Benzoyl-2,3-dihydro-1 H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)- 1,3-propanediol (1:1). [74103-07-4].



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	14-JUL-2003	Adequate
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Toradol Injection, 15 mg/mL and 30 mg/mL	19-698	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	N/A		
Labeling	Deficient	31-JUL-2003	J.Barlow
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt Yes ___X___ No _____

If no, explain reason(s) below:

SPOT? Yes___ No__X

V:\FIRMSAM\APOTEX\LTRS&REV\76722.R01.doc

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-722

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry manufacturing and controls are not approvable. It is recommended that a Not Approvable, MINOR, letter be sent to the applicant.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug is Toradol Injections 15 mg/mL and 30 mg/mL manufactured by Roche Palo (NDA no. 19-698). The active ingredient in Toradol Injections is Ketorolac Tromethamine which is a NSAID.

Adult Patients: Ketorolac Tromethamine is indicated for the short-term (</=5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. : Ketorolac Tromethamine is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses. Patients should be switched to alternative analgesics as soon as possible, but : Ketorolac Tromethamine therapy is not to exceed 5 days.

Pediatric Patients: The safety and effectiveness of single doses of : Ketorolac Tromethamine IV/IM have been established in pediatric patients between the ages of 2 and 16 years. : Ketorolac Tromethamine, as a single injectable dose, has been shown to be effective in the management of moderately severe acute pain that requires analgesia at the opioid level, usually in the postoperative setting. There is limited data available to support the use of multiple doses of : Ketorolac Tromethamine in pediatric patients. Safety and effectiveness have not been established in pediatric patients below the age of 2 years.

The chemical name for : Ketorolac Tromethamine is (±)-5-Benzoyl-2,3-dihydro-1 H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)- 1,3-propanediol (1:1). [74103-07-4].
Its empirical formula is $C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$ and its molecular weight is 376.40
Each mL of Ketorolac Tromethamine injection contains either 15 mg or 30 mg of Ketorolac Tromethamine as the active ingredient and the inactive ingredients in the solution are as follows: Sodium Chloride, Alcohol, Hydrochloric acid, Sodium Hydroxide and Water for Injection.

The firm has filed a waiver request for the Bioavailability/Bioequivalence study (see page 240). The formulation is same as the Reference Listed Drug- Toradol.

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1 (page 8)

Both the drug product and the drug substance are compendial items. The firm has used the USP method for Assay and Related substance for the Drug Substance and Drug product.

This ANDA is found to be deficient and the deficiencies are highlighted in bold letters in the text. The deficiencies noted will be communicated to the applicant.

B. Description of How the Drug Product is Intended to be Used

IV/IM injection, used in the management of moderately severe acute pain that requires analgesia at the opioid level, usually in the postoperative setting. There is limited data available to support the use of multiple doses of Ketorolac Tromethamine in pediatric patients. Safety and effectiveness have not been established in pediatric patients below the age of 2 years.

C. Basis for Approvability or Not-Approval Recommendation

Firm needs to resolve issues related to drug substance and drug product specifications and other deficiencies as noted in the deficiency letter.

APPEARS THIS WAY
ON ORIGINAL

III. Administrative

A. Reviewer's Signature

Yusuf Amin

B. Endorsement Block

Yusuf Amin/Chemist/8/21/03 9/17/03
Al Mueller, Ph.D./Chemistry Team Leader/8/21/03 9-19-03
Craig Kiester/Project Manager/ 9/22/03

C. CC Block: N/A

APPEARS THIS WAY
ON ORIGINAL

Redacted 24 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

7.

8.

9.

B. Comments:

1. The bioequivalence information which you have provided is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

2. Labeling deficiencies have been communicated to you previously . Your response should address these deficiencies.

3. Please provide updated room temperature stability data tables on the ANDA exhibit batches.

4. The Microbiological information which you have provided is under review. Any deficiencies found will be communicated to you under a separate cover.

5. We have noted that you intend to discontinue full testing of API after -lots. Reduction in testing of API is done based on vendor qualification SOP in consultation with the local district of the agency.

6. The firms referenced in your ANDA application relative to the manufacturing, packaging and testing of the product must be in compliance with cGMP's at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

Sincerely yours,

10-1-03

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-722
ANDA DUP 76-722
DIV FILE
Field Copy

Endorsements:

HFD-623/Y.Amin/8/21/03 9/17/03 9/29/03
HFD-623/A. Mueller/8/21/03 9-30-03
HFD-617/C.Kiester/9/12/03 9/12/03

V:\FIRMSAM\APOTEX\LTRS&REV\76722.R01.doc
F/T by: ard/9/16/03

CHEMISTRY REVIEW- NOT APPROVABLE (MINOR).

#2

ANDA 76-722

Ketorolac Tromethamine Injection USP, 15 mg/mL and 30 mg/mL - Syringe

Apotex Corporation

Yusuf Amin
Chemistry Division I

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. ANDA 76-722

2. REVIEW #: 2

3. REVIEW DATE: 12 JAN 2004

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	11-APR-2003
Amendment	22-MAY-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	23-DEC-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Corporation
Address:	616 Heathrow Drive Lincolnshire, IL 60069
Representative:	Marcy Macdonald
Telephone:	(847) 279 7740

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Ketorolac Tromethamine

9. LEGAL BASIS FOR SUBMISSION: Under section 505(j)(1) of FFD &CA.
   Toradol Injection, 15 mg/mL and 30 mg/mL, the subject of NDA 19-698 held by Roche Palo.

The firm certifies that to the best of its knowledge, all patents related to Toradol Injection, 15 mg/mL and 30 mg/mL, held by Roche Palo have expired. The firm also certifies that in its opinion and to the best of its knowledge, there is no market exclusivity currently in effect for the listed drug, Toradol Injection, 15 mg/mL and 30 mg/mL.

Since this application was filed, NDA 19-698 has been withdrawn by Roche Palo and new reference listed drugs are Bedford's ANDA 75-222 and ANDA 75-228 for the two strengths of drug product. There are no exclusivities nor unexpired patents for these two ANDA's.

10. PHARMACOL. CATEGORY: NSAID (**N**on Steroidal Anti-Inflammatory Drug)

11. DOSAGE FORM: Parenteral Solution for Administration by IV/IM Injection (Single-dose Syringe Unpreserved)

12. STRENGTH/POTENCY: 15 mg/mL and 30mg/mL

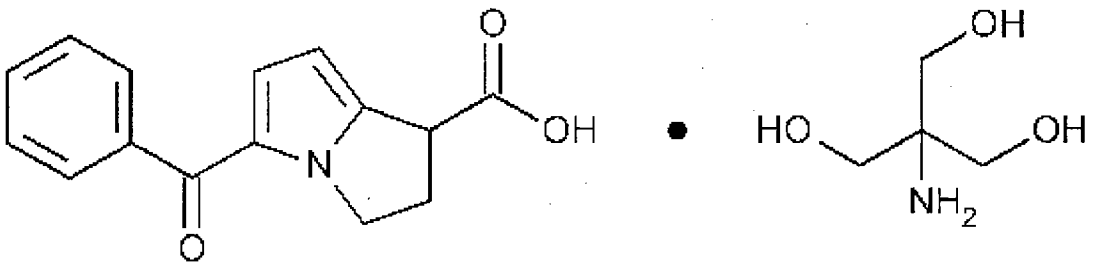
13. ROUTE OF ADMINISTRATION: IV/IM Injection

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

_X_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Ketorolac Tromethamine
$C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$ 376.40
1H-Pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, (±)-, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).
(±)-5-Benzoyl-2,3-dihydro-1 H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)- 1,3-propanediol (1:1). [74103-07-4].



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	07-JUL-2004	Adequate
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA for Ketorolac Tromethamine Injection, 15 mg/mL and 30 mg/mL	75-222	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	26-APR-2004	B. Pillari
EES	Acceptable	21-JUN-2004	S. Adams
Methods Validation	N/A		
Labeling	Acceptable	27-FEB-2004	J.Barlow
Bioequivalence	Acceptable	20-NOV-2003	P.Bush
EA	Acceptable	15-JUL-2003	Y.Amin
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. _X__ Yes ____ No If no, explain reason(s) below:

V:\FIRMSAM\APOTEX\LTRS&REV\76722.REV2.doc

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-722

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Chemistry manufacturing and controls are approvable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug is Ketorolac Tromethamine 15 mg/mL and 30 mg/mL manufactured by Bedford (ANDA no. 75-222). The active ingredient is Ketorolac Tromethamine which is a NSAID.

Adult Patients: Ketorolac Tromethamine is indicated for the short-term (</=5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. : Ketorolac Tromethamine is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses. Patients should be switched to alternative analgesics as soon as possible, but : Ketorolac Tromethamine therapy is not to exceed 5 days.

Pediatric Patients: The safety and effectiveness of single doses of : Ketorolac Tromethamine IV/IM have been established in pediatric patients between the ages of 2 and 16 years. : Ketorolac Tromethamine, as a single injectable dose, has been shown to be effective in the management of moderately severe acute pain that requires analgesia at the opioid level, usually in the postoperative setting. There is limited data available to support the use of multiple doses of : Ketorolac Tromethamine in pediatric patients. Safety and effectiveness have not been established in pediatric patients below the age of 2 years.

The chemical name for : Ketorolac Tromethamine is (±)-5-Benzoyl-2,3-dihydro-1 H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)- 1,3-propanediol (1:1). [74103-07-4].
Its empirical formula is $C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$ and its molecular weight is 376.40
Each mL of Ketorolac Tromethamine injection contains either 15 mg or 30 mg of Ketorolac Tromethamine as the active ingredient and the inactive ingredients in the solution are as follows: Sodium Chloride, Alcohol, Hydrochloric acid, Sodium Hydroxide and Water for Injection.

The manufacturing ——— of the injections in syringes are done at Gland Pharma, Hyderabad, India and testing of the Drug substance and finished products are done at the applicant's facility at Vernon Hills, Illinois and alternatively at ——— ——— The excipients and packaging components are tested at ——— ——— Size of the commercial batch is ——— for 15 mg/mL and for 30 mg/mL the commercial size batches are——— and ——— The ANDA batch for 15

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2 (page 8)

patients. Safety and effectiveness have not been established in pediatric patients below the age of 2 years.

C. Basis for Approvability or Not-Approval Recommendation
Approvable.

APPEARS THIS WAY
ON ORIGINAL

III. Administrative

A. Reviewer's Signature

Yusuf Amin

B. Endorsement Block

Yusuf Amin/Chemist/1/14/04 6/23/04
Al Mueller, Ph.D./Chemistry Team Leader/ 7-7-04
Craig Kiester/Project Manager/ 7/8/04

C. CC Block: N/A

APPEARS THIS WAY
ON ORIGINAL

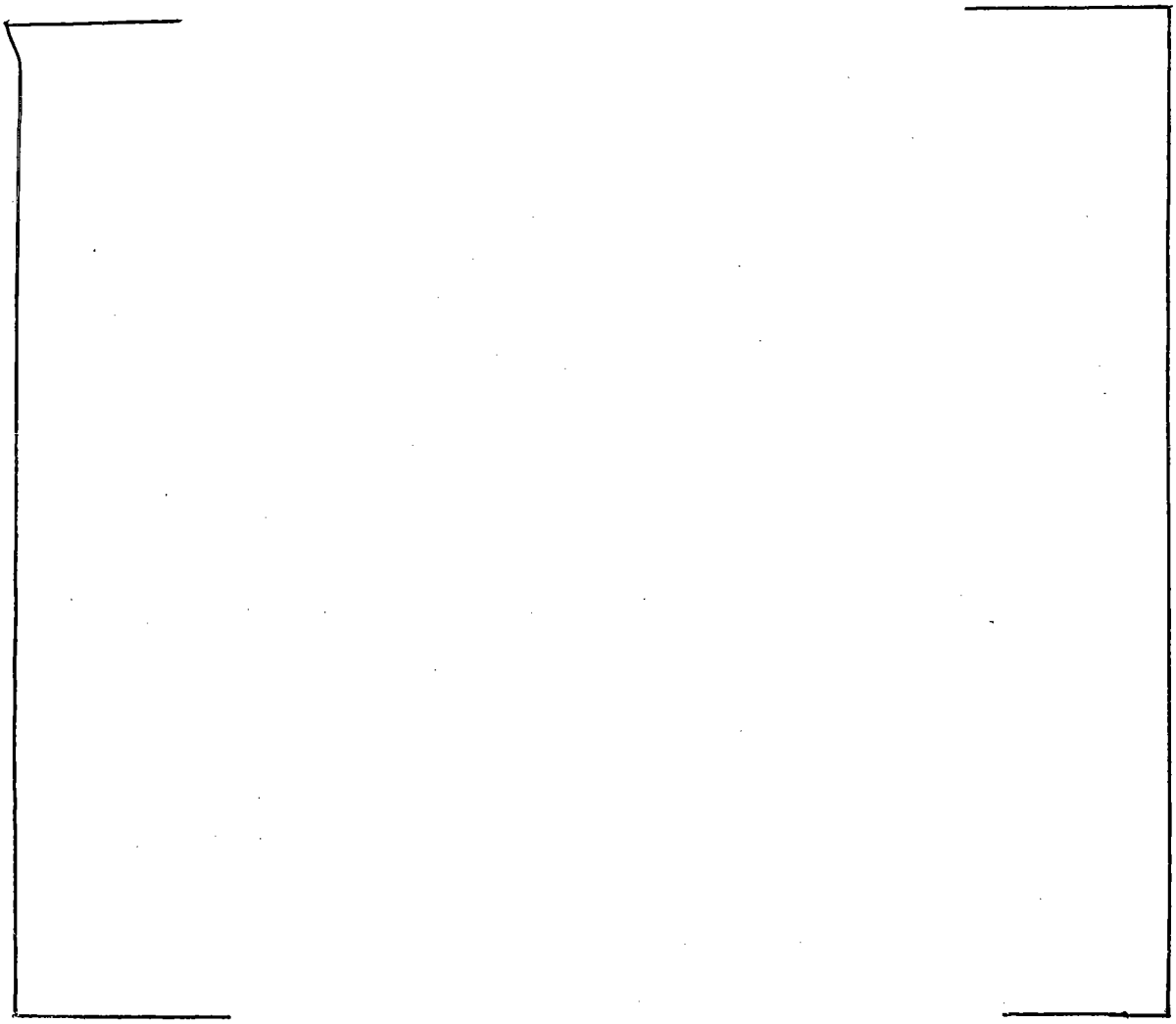
Redacted 21 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2



30. MICROBIOLOGY: **Satisfactory** (26-APR-2004, B. Pillari)

31. SAMPLES AND RESULTS **N/A**
The API and the Drug Product are compendial.

32. LABELING: **Satisfactory** (J. Barlow, 27-FEB-2004)

33. ESTABLISHMENT INSPECTION **Satisfactory** (Dated 21-JUN-2004, S. Adams)

34. BIOEQUIVALENCY STATUS **Acceptable** 20-NOV-2003, P. Bush.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory
Provided, Volume 1.4, Section XIX.

36. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt Yes ___X___ No _____

If no, explain reason(s) below:

SPOT? Yes___ No__X

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-722

BIOEQUIVALENCE REVIEW(S)

Ketorolac Tromethamine Injection, USP
15 mg/mL (1 mL syringe)
30 mg/mL (1 mL and 2 mL syringes)
ANDA # 76-722
Reviewer: Phelicia B. Bush
v:\firmsam\apotoex\ltrs&rev\76722W0403.doc

Apotex Corp
50 Lakeview Parkway
Suite 127
Vernon Hills, Il 60061
Submission Date: April 11, 2003

Review of Waiver Requests

Executive Summary

This application consisted of waiver requests of *in* vivo bioequivalence study requirements for the test products, Ketorolac Tromethamine Injection, USP 15 mg/mL (1 mL syringe) and 30 mg/mL (1 mL and 2 mL syringes). The reference listed drug is Toradol® IV/IM 15 mg/mL and 30 mg/mL (Roche Laboratories). Based on the information submitted, the test products fall under 21 CFR 320.22 (b) (1) of the Bioavailability/Bioequivalence Regulations. The waivers of the *in* vivo bioequivalence study requirements are granted.

Background

The firm has submitted requests for waivers of *in vivo* bioavailability/bioequivalance study requirements under the provisions of 21 CFR 320.22 (b) (1) for its proposed products, Ketorolac Tromethamine Injection, USP 15 mg/mL (1 mL syringe) and 30 mg/mL (1 mL and 2 mL syringes). The corresponding RLD listed in Orange Book 2003 is Toradol® IV/IM 15 mg/mL and 30 mg/mL (NDA 19-698), manufactured by Roche Laboratories.

Toradol® IV/IM, a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs), is indicated for the short-term (up to 5 days in adults) management of moderately severe acute pain that requires analgesia at the opioid level. It is available for intravenous (IV) or intramuscular (IM) administration as: 15 mg in 1 mL and 30 mg in 1 mL sterile solution; 60 mg of ketorolac tromethamine in 2 mL sterile solution is available for IM administration only.

The Division of Bioequivalence has reviewed several ANDAs for this product including ANDA 74-801, ANDA 74-802, ANDA 74-993, ANDA 75-222, ANDA 75-784, ANDA 75-631, ANDA 75-626, ANDA 75-299, and ANDA 75-228.

Formulation Comparison

Ingredient	Reference Roche Laboratories' Toradol® IV/IM 15 mg/mL	Test Apotex Corp.'s Ketorolac Tromethamine Injection, USP 15 mg/mL
	Amount per ml (mg)	Amount per ml (mg)
Ketorolac Tromethamine, USP	15	15
Alcohol (95%), USP	100	100
Sodium Chloride, USP	6.68	6.68
Hydrochloric Acid, NF	As required to adjust pH	As required to adjust pH
Sodium Hydroxide, NF	As required to adjust pH	As required to adjust pH
Water For Injection, USP	Quantity Sufficient	Quantity Sufficient
[redacted]	[redacted]	[redacted]

Ingredient	Reference Roche Laboratories' Toradol® IV/IM 30 mg/mL	Test Apotex Corp.'s Ketorolac Tromethamine Injection, USP 30 mg/mL
	Amount per ml (mg)	Amount per ml (mg)
Ketorolac Tromethamine, USP	30	30
Alcohol (95%), USP	100	100
Sodium Chloride, USP	4.35	4.35
Hydrochloric Acid, NF	As required to adjust pH	As required to adjust pH
Sodium Hydroxide, NF	As required to adjust pH	As required to adjust pH
Water For Injection, USP	Quantity Sufficient	Quantity Sufficient
[redacted]	[redacted]	[redacted]

Comments

1) The test products, Ketorolac Tromethamine Injection, USP 15 mg/mL and 30 mg/mL are sterile parenteral solutions intended solely for administration by injection and contain the same active and inactive ingredients in the same concentration as the reference product, Toradol® IV/IM 15 mg/mL and 30 mg/mL.

2) The test products meet the requirements for a waiver of *in vivo* bioequivalence study as stated in 21 CFR 320.22 (b) (1).

Recommendation

The information submitted by Apotex Corp. on Ketorolac Tromethamine Injection, USP 15 mg/mL (1 mL syringe) and 30 mg/mL (1 mL and 2 mL syringes) falls under 21 CFR 320.22 (b) (1) of the Bioavailability/Bioequivalence Regulations. The waivers of *in vivo* bioequivalence study requirements for Ketorolac Tromethamine Injection, USP 15 mg/mL (1 mL syringe) and 30 mg/mL (1 mL and 2 mL syringes) are granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test products, Ketorolac Tromethamine Injection, USP 15 mg/mL (1 mL syringe) and 30 mg/mL (1 mL and 2 mL syringes) to be bioequivalent to Toradol® IV/IM 15 mg/mL (1 mL vial) and 30 mg/mL, (1 mL and 2 mL vials) manufactured by Roche Laboratories.

Phelicia B. Bush, Pharm.D. Phelicia B. Bush 11/20/03
Review Branch III
Division of Bioequivalence

RD INITIALED GJP Singh, Ph.D.
FT INITIALED GJP Singh, Ph.D. Date 11-20-03

Concur: Barbara M Davit Date 11/20/03
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA# 76-722 (original, duplicate), Bush, HFD-658 Singh, HFD-658, Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 76-722 APPLICANT: Apotex Corp.

DRUG PRODUCT: Ketorolac Tromethamine Injection, USP
15 mg/mL (1 mL syringe)
30 mg/mL (1 mL and 2 mL syringes)

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

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

Sincerely yours,

for Barbara M. Davit

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

CC: ANDA # 76-722
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: P. Bush

V:\FIRMSAM\APOTEX\LTRS&REV\76722W0403.DOC
Printed in final on November 20, 2003

Endorsments: (Final with Dates)
HFD-658/ P. Bush 11/20/03
HFD-658/ GJP. Singh 11-20-03
HFD-650/ D. Conner 11/20/03
HFD-617/ S. Mazzella

Bioequivalency - Acceptable

Submission Date: April 11, 2003

1) Waiver (WAI)

Strength: 15 mg/mL
Outcome: AC

2) Waiver (WAI)

Strength: 30 mg/mL
Outcome: AC

Outcome Decisions: AC- Acceptable
Winbio comments: Waivers are granted

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-722 SPONSOR : Apotex Corp.

DRUG AND DOSAGE FORM : Ketorolac Tromethamine Injection, USP

STRENGTH(S) : 15 mg/mL (1mL syringe) and 30 mg/mL (1 mL and 2 mL syringes)

TYPES OF STUDIES : SD SDF MULT OTHER

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A

DISSOLUTION : N/A

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Phelicia B. Bush, Pharm.D. BRANCH : III

INITIAL : PBush DATE : 11/20/03

TEAM LEADER : GJP SINGH, Ph.D. BRANCH : III

INITIAL : GJP Singh DATE : 11-20-03

for

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

INITIAL : Barbara M. Davit DATE : 11/20/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-722

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review
Review for HFD-620

29 October 2003

ANDA: 76-722

Drug Product Name
Proprietary: Toradol®
Non-proprietary: Ketorolac Tromethamine Injection USP
Drug Product Classification: N/A

Review Number: 1

Subject of this Review
Submission Date: April 11, 2003
Receipt Date: April 17, 2003
Consult Date: N/A
Date Assigned for Review: October 10, 2003

Submission History (for amendments only)
Date(s) of Previous Submission(s): None
Date(s) of Previous Micro Review(s): None

Applicant/Sponsor
Name: Apotex Corp.
Address: 616 Heathrow Drive, Lincolnshire, IL 60069
Representative: Marcy Macdonald, Director, Regulatory Affairs
Telephone: 847-279-7740

Name of Reviewer: Brenda Pillari

Conclusion: This submission is not recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR: N/A**

3. **MANUFACTURING SITE:**
Gland Pharma
D.P. Nally
Hyderabad 500 043 R.R. Dist.
India

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 15mg/mL (1mL syringe); 30mg/mL (1mL and 2mL syringes)

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** NSAID Analgesic Agent

B. **SUPPORTING/RELATED DOCUMENTS:**

DMF [redacted]

DMF

DMF

DMF

DMF

C. **REMARKS:**
TORADOL is supplied in a TUBEX® Sterile Cartridge-Needle Unit or a sterile vial whereas KETROLAC is available in a pre-filled syringe.

A plunger rod component is mentioned (Vol. 1.3, p. 981) with no associated DMF. The plunger rod is not attached to the plunger stopper during syringe filling – see requested sample.

filename: v:microrev\76-722.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
This submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment" and "H. List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -
The drug solution is sterilized by [redacted]. The syringes are sealed with plunger stopper.

The glass syringes are [redacted]

B. Brief Description of Microbiology Deficiencies -
Various deficiencies including (but not limited to):

- lack of critical equipment information;
- lack of depyrogenation data for the container/closure; system
- incomplete environmental monitoring information.

C. Assessment of Risk Due to Microbiology Deficiencies -
Moderate

III. Administrative

A. Reviewer's Signature Brenda Pillari

B. Endorsement Block
Microbiologist / Brenda Pillari
Microbiology Team Leader / Neal Sweeney
Neal J Sweeney 12-23-03

C. CC Block
cc: HFD- 620/Division File/ANDA 76-722

Redacted 13 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #1

Product Quality Microbiology Review
Review for HFD-620

April 21, 2004

ANDA: 76-722

Drug Product Name
Proprietary: Toradol®
Non-proprietary: Ketorolac Tromethamine Injection USP
Drug Product Classification: N/A

Review Number: 2

Subject of this Review
Submission Date: March 17, 2004
Receipt Date: March 19, 2004
Consult Date: N/A
Date Assigned for Review: March 25, 2004

Submission History (for amendments only)
Date(s) of Previous Submission(s): April 17, 2003 (accepted for filing)
Date(s) of Previous Micro Review(s): October 29, 2003

Applicant/Sponsor
Name: Apotex Corp.
Address: 616 Heathrow Drive, Lincolnshire, IL 60069
Representative: Marcy Macdonald, Director, Regulatory Affairs
Telephone: 847-279-7740

Name of Reviewer: Brenda Pillari

Conclusion: This submission is recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR: N/A**

3. **MANUFACTURING SITE:**
Gland Pharma
D.P. Nally
Hyderabad 500 043 R.R. Dist.
India

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 15mg/mL (1mL syringe); 30mg/mL (1mL and 2mL syringes)

5. **METHOD(S) OF STERILIZATION:** ———————

6. **PHARMACOLOGICAL CATEGORY:** NSAID Analgesic Agent

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:**
The subject amendment (March 17, 2004) is a response to microbiology deficiency letter dated January 5, 2004.

filename: v:microrev\76-722a1.doc

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
This submission is recommended for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -
The drug solution is sterilized by [redacted] The syringes are sealed with plunger stopper.

The glass syringes are [redacted]

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – The public health risk associated with these products is minimal. No product quality microbiology deficiencies were identified.

III. Administrative

A. Reviewer's Signature Brenda Pillari

B. Endorsement Block
Microbiologist / Brenda Pillari
Microbiology Team Leader / Neal Sweeney Neal J Sweeney 4-26-04

C. CC Block
cc: ANDA 76-722a1/Field Copy/Division File

Redacted 5 page(s)

of trade secret and/or

confidential commercial

information from

MICROBIOLOGY REVIEW #2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-722

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-722 Applicant Apotex

Drug Ketorolac Tromethamine Strength(s) ~~15mg/ml, 30mg/ml~~ 5/ml

APPROVAL **TENTATIVE APPROVAL** **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** **OTHER**

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. Martin Shimer Chief, Reg. Support Branch	Date_____ Initials_____	Date_____ Initials_____

Contains GDEA certification: Yes No (required if sub after 6/1/92)

Determ. of Involvement? Yes No

Pediatric Exclusivity System

RLD = NDA#_____

Patent/Exclusivity Certification: Yes No

Date Checked _____

If Para. IV Certification- did applicant Nothing Submitted

Notify patent holder/NDA holder Yes No Written request issued

Was applicant sued w/in 45 days: Yes No Study Submitted

Has case been settled: Yes No Date settled:

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes No

Type of Letter:

Comments:

2. Project Manager, Sim Eng Team 1 Review Support Branch	Date 7/8/04 Initials ★	Date_____ Initials_____

Original Rec'd date 4/11/03

Date Acceptable for Filing 4/17/03 J

Patent Certification (type) 2

Date Patent/Exclus.expires N/A

Citizens' Petition/Legal Case Yes (No)

(If YES, attach email from PM to CP coord)

First Generic Yes (No)

Acceptable Bio reviews tabbed (Yes) No

Suitability Petition/Pediatric Waiver N/A

Pediatric Waiver Request Accepted Rejected Pending

EER Status Pending ~~Acceptable~~ OAI

Date of EER Status 6/21/04

Date of Office Bio Review 11/20/03

Date of Labeling Approv. Sum 3/2/04

Date of Sterility Assur. App. 4/26/04

Methods Val. Samples Pending Yes No N/A

MV Commitment Rcd. from Firm Yes No

Modified-release dosage form: Yes No N/A

Interim Dissol. Specs in AP Ltr: Yes N/A

Previously reviewed and tentatively approved Date N/A

Previously reviewed and CGMP def. /NA Minor issued Date N/A

Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included OGD Regulatory Counsel, Post-MMA Language Included Comments:	Date _____ Initials_____

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III Comments:	Date 7/20 Initials RS

CMC OK

Updated DMF has been received - OK

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-722 Applicant Apotex Strength(s) ~~15mg/ml, 30mg/ml~~ 5ml syrup

Drug ketorolac tromethamine

APPROVAL **TENTATIVE APPROVAL** **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** **OTHER**

REVIEWER: **DRAFT Package** **FINAL Package**

1. ~~Martin Shimer~~ Paras Patel
Chief, Reg. Support Branch
Date _____ Initials _____
Date 7/12/04 Initials P.M.P

Contains GDEA certification: (Yes) No
(required if sub after 6/1/92)

Patent/Exclusivity Certification: (Yes) PII No

If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ~~No~~ NA
Was applicant sued w/in 45 days: Yes ~~No~~ NA
Has case been settled: Yes No
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes (No)

Determ. of Involvement? Yes (No)
Pediatric Exclusivity System
RLD = NDA# _____
Date Checked _____
Nothing Submitted
Written request issued
Study Submitted
Date settled:

Type of Letter: * RLD Toradol (N) 19698 currently in discontinued section removed for safety or efficacy
Comments: OB. FR notice regarding issue of "safety or efficacy" still pending. - Ready for Full Approval once FR notice is completed and RLD not

2. Project Manager, Jim Eng Team 1
Review Support Branch
Date 7/8/04 Initials _____
Date _____ Initials _____

Original Rec'd date 4/11/03
Date Acceptable for Filing 4/17/03
Patent Certification (type) 2
Date Patent/Exclus.expires N/A
Citizens' Petition/Legal Case Yes (No)
(If YES, attach email from PM to CP coord)
First Generic Yes (No)
Acceptable Bio reviews tabbed (Yes) No
Suitability Petition/Pediatric Waiver N/A
Pediatric Waiver Request Accepted Rejected Pending

EER Status Pending ~~Acceptable~~ OAI
Date of EER Status 6/21/04
Date of Office Bio Review 11/20/03
Date of Labeling Approv. Sum 3/2/04
Date of Sterility Assur. App. 4/26/04
Methods Val. Samples Pending Yes No N/A
MV Commitment Rcd. from Firm Yes No
Modified-release dosage form: Yes No N/A
Interim Dissol. Specs in AP Ltr: Yes N/A

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

3. David Read **(PP IVs Only)** Pre-MMA Language included
OGD Regulatory Counsel, Post-MMA Language Included
Comments:
N/A
Date _____
Initials _____

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments:
See next page
Date _____
Initials _____

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for this drug product.

6. Vacant Former RLD = Tradol Injection 15mg/mL & 30mg/mL Date_____
Deputy Dir., DLPS Syntex (USA) Inc NDA 19-698 Initials_____

7. Peter Rickman Date 7/27/04 for
Director, DLPS Initials_____
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes / No ; Petition: Yes / No
Comments: Acceptable EES dated 6/21/04 (certified 7/27/04) NO OAI Alerts noted. Bioequivalence waiver (to Syntex RLD) granted under 21 CFR 320.22(b)(1) Drug product is "Q1Q" to the Syntex RLD. Office Level Discussed 11/20/03 FTE found acceptable for approval 3/16/04 Microbiology/Sterility/assurance found acceptable 4/26/04. CMC found acceptable for approval 7/7/04. Methods validation is not required - both the API and drug product are compendial

8. Robert L. West 7/27/2004
Deputy Director, OGD Initials Robert West
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes / No
Comments: The original RLD for this ANDA, Syntex's Tradol Injection, is currently in the discontinued section of the Orange Book. The agency has made the determination that Syntex's product was not withdrawn from the market for safety or effectiveness reasons. This determination will publish in the FR. The current RLD is Bedford Laboratories ANDA 75-222 (001)(002)
This ANDA is recommended for approval.

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:
First Generic Approval PD or Clinical for BE Special Scientific or Reg.Issue

10. Project Manager, Team Simon Ong Date 7/27/04
Review Support Branch Initials _____
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
9AM Time notified of approval by phone 9:18 AM Time approval letter faxed
FDA Notification:
7/27 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
7/27 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-722

CORRESPONDENCE

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

Concur. 5/30/03 505(j)(2)(A)

April 11, 2003

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Ketorolac Tromethamine Injection, USP
15 mg/mL and 30 mg/mL - Syringes
Original Abbreviated New Drug Application

To Whom It May Concern:

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1994, Apotex Corp., hereby submits an original abbreviated new drug application (ANDA) for Ketorolac Tromethamine Injection, USP 15 mg/mL (1 mL syringe) and 30 mg/mL (1 mL and 2 mL syringes).

We are submitting an archival copy under blue cover, a chemistry review and two additional copies of the analytical methods section under red cover, and the bioavailability/bioequivalence review section under orange cover.

Apotex Corp. hereby certifies that in accordance with 21 CFR 314.94(d)(5), a true field copy of the technical sections of this submission under a burgundy cover is also included.

We appreciate an expeditious review of this application. Please direct any inquiries regarding this application to me at the addresses listed above.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
APR 17 2003
OGD / CDER

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

May 22, 2003

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 76-722
Ketorolac Tromethamine Injection, USP
15 mg/mL and 30 mg/mL - Syringes

~~NEW CORRESP~~
NC

REQUEST FOR ADDITIONAL INFORMATION

To Whom It May Concern:

Per a telephone conversation on May 22, 2003 between Marcy Macdonald (Apotex Corp.) and Arianne Camphire (FDA Regulatory Support, Project Manager) Apotex Corp., hereby submits this amendment to our original application, submitted April 11, 2003, for the following:

The Reference Listed Drug applicant has changed from Syntex (USA) Inc. LLC to Roche Palo. Therefore included in this amendment are:

- An updated 356h form, original ANDA page 1
- An updated Basis for ANDA Submission, original ANDA pages 4-6

Also included in this amendment is a revised Stability Commitment statement. This statement was revised to reflect the correct storage orientation as horizontal. The original ANDA page 1719 stated to be stored "in both the inverted and vertical positions."

Apotex Corp. hereby certifies that in accordance with 21 CFR 314.96(b), a true field copy will be sent to the Office of Generic drugs.

Please direct any inquiries regarding this amendment to me at the addresses listed above.

Sincerely,

Marcy Macdonald
Director, Regulatory Affairs
(847) 279-7740

RECEIVED
MAY 27 2003
OGD / CDER

ANDA 76-722

JUN - 3 2003

Apotex Corp.
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite #127
Vernon Hills, IL 60061

Dear Madam:

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

Reference is made to the telephone conversation dated May 22, 2003 and your correspondence dated May 22, 2003.

NAME OF DRUG: Ketorolac Tromethamine Injection USP, 15 mg/mL, 1 mL syringes and 30 mg/mL, 1 mL and 2 mL syringes

DATE OF APPLICATION: April 11, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 17, 2003

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

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

Should you have questions concerning this application, contact:

Craig Kiester
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

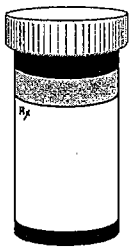
Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-722
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSB 02-JUN-2003 date
HFD-615/ACamphire, CSO Arianne Camphire date 02-JUN-2003
Word File
V:\FIRMSAM\Apotex\LTRS&REV\76722.ACK
F/T

ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Apotex Corp. (Attention: Marcy MacDonald)
Phone: 847-279-7740 **Fax: 847-353-2982**

From: Jim Barlow
Fax: 301-443-3847 **Phone:** 301-827-5830

Number of Pages (including cover sheet): 21 **Date:** 7/31/03

Comments:

Dear Ms. MacDonald,

Here is the copy of the label deficiency referencing your ANDA 76-722 submission. Please revise and send 12 copies of final printed labels and labeling. Please send a courtesy copy to my attention. The courtesy copy should include as least one final printed copy of labels and labeling. Call with questions.

Sincerely,
Jim Barlow

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

ANDA Number:	76-722
Date of Submission:	April 11, 2003
Applicant's Name:	Apotex Corp.
Established Name:	Ketorolac Tromethamine Injection USP, 15 mg/mL, 30 mg/mL and 60 mg/2mL

Labeling Deficiencies:

1. **CONTAINER – 1mL and 2 mL pre-filled syringes**
   Satisfactory in **draft** as of the April 11, 2003 submission

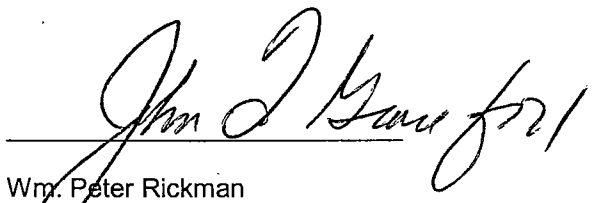
2. **CARTON – 10's**
   Satisfactory in **draft** as of the April 11, 2003 submission

3. **PACKAGE INSERT**
   Attached you will find mocked-up package insert labeling. Revise accordingly.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

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

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



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

Attached: Copy of mocked-up package insert labeling

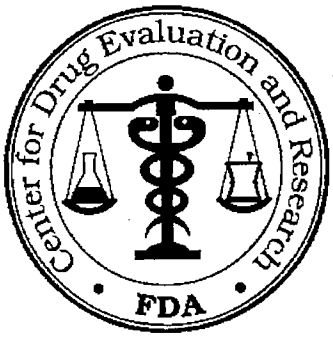
19 pages of draft labeling were removed from this portion of the document

MINOR AMENDMENT

ANDA 76-722

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

OCT - 2 2003



APPLICANT: Apotex Corp.

TEL: 847-279-7740

ATTN: Marcy Macdonald

FAX: 847-353-2982

FROM: Craig Kiester

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated April 11, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ketorolac Tromethamine Injection USP, 15 mg/mL, 30 mg/mL and 60 mg/2mL syringes.

Reference is also made to your amendment(s) dated: .

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

36. Chemistry Comments to be provided to the Applicant

ANDA: 76-722 APPLICANT: Apotex Corporation OCT - 2 2003

DRUG PRODUCT: Ketorolac Tromethamine Injection USP, 15 mg/mL and 30 mg/mL Syringe

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]

7.

8.

9.

B. Comments:

1. The bioequivalence information which you have provided is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

2. Labeling deficiencies have been communicated to you previously . Your response should address these deficiencies.

3. Please provide updated room temperature stability data tables on the ANDA exhibit batches.

4. The Microbiological information which you have provided is under review. Any deficiencies found will be communicated to you under a separate cover.

5. We have noted that you intend to discontinue full testing of API after – lots. Reduction in testing of API is done based on vendor qualification SOP in consultation with the local district of the agency.

6. The firms referenced in your ANDA application relative to the manufacturing, packaging and testing of the product must be in compliance with cGMP's at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

ORIG AMENDMENT

N/APM

December 23, 2003

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

RE: Ketorolac Tromethamine Injection, USP
15 mg/mL and 30 mg/mL - Syringes
ANDA No. 76-722

To Whom It May Concern:

Apotex Corp. is submitting in triplicate (Archive, Review and Field) a minor amendment in response to the FDA minor deficiency letter dated October 02, 2003 for the above referenced product.

If you have questions please do not hesitate to contact me at 847-279-7740.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

RECEIVED

DEC 2 4 2003

OGD / CDER

FAX Cover Sheet – Microbiology Deficiencies Enclosed

Office of Generic Drugs, CDER, FDA

Document Control Room, Metro Park North II

7500 Standish Place, Room 150

Rockville MD 20855-2773 (301-594-0320)

TO: Marcy Macdonald		**FROM:** Bonnie McNeal
Apotex Corp.		Microbiology Project Manager
PHONE: 847-279-7740		**PHONE:** (301) 827-0530
FAX: 847-353-2982		**FAX:** (301) 827-5911

Total number of pages, excluding this cover sheet: 2

Date: January 5, 2004

Microbiology Deficiencies:

Enclosed are the microbiology deficiencies for ANDA 76-722. The submission reviewed was submitted on "April 11, 2003". Please respond to this letter as soon as possible. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter.

Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

If you have questions, feel free to call me.

Bonnie

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

FDA FAX 1/5/2004

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

ORIG AMENDMENT

AF

February 10, 2004

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

RE: Ketorolac Tromethamine Injection, USP
15 mg/mL, 30 mg/mL and 60 mg/2mL - Syringes
ANDA No. 76-722

To Whom It May Concern:

Apotex Corp. is submitting in duplicate a labeling amendment in response to the FDA labeling deficiency letter dated July 31, 2003 for the above referenced product.

If you have questions, please do not hesitate to contact me at 847-279-7740.

Sincerely,

for

Marcy Macdonald
Director, Regulatory Affairs

RECEIVED
FEB 12 2004

APOTEX CORP.

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

March 17, 2004

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AS

MICROBIOLOGY AMENDMENT

RE: Ketorolac Tromethamine Injection, USP
15 mg/mL and 30 mg/mL - Syringes
ANDA No. 76-722

To Whom It May Concern:

Apotex Corp. is submitting in triplicate (Archive, Review and Field) a microbiology amendment in response to the FDA microbiology deficiency letter dated January 05, 2004 regarding the above referenced product.

If you have questions please do not hesitate to contact me at 847-279-7740.

Sincerely,

for Marcy Macdonald
Director, Regulatory Affairs

RECEIVED
MAR 19 2004
OGD/CDER