CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-284

Generic Name: Ketorolac Tromethamine Tablets, USP

Sponsor: Sidmak Laboratories, Inc.

Approval Date: June 23, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-284

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

ANDA 75-284

JUN 23 1999

Sidmak Laboratories Inc.
Attention: Deborah L. Pakay
17 West Street
P.O. Box 371
East Hanover, New Jersey 07936

Dear Madam:

This is in reference to your abbreviated new drug application dated December 23, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ketorolac Tromethamine Tablets USP, 10 mg.

Reference is also made to your amendments dated June 9 and October 9, 1998; March 15, May 27 and May 28, 1999.

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 Tablets USP, 10 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Toradol® Tablets, 10 mg of Syntex Laboratories Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVED FINAL LABELING

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**).

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

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 3-fold from 5.4 to 17.8 mcg/h/mL) and terminal half-life increased approximately 2-fold from 6.6 to 15.1 hours. Therefore, concomitant use of ketorolac tromethamine and probenecid is contraindicated.

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.

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.

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

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

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

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

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 q.i.d., 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 mcg/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 musculature, thus increasing the risk of uterine hemorrhage (see **CONTRAINDICATIONS**).

Lactation and Nursing: After a single administration of 10 mg of 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 one day of dosing (q.i.d.), 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 efficacy in pediatric patients (less than 16 years of age) have not been established. Therefore, use of ketorolac tromethamine in pediatric patients is not recommended.

Use in the Elderly (≥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. The incidences 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 G.I. 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.

Incidence 1% or less:

Body as a Whole: weight gain, fever, infections, asthenia.

Cardiovascular: palpitation, pallor, 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**), myalgia.

Cardiovascular: hypotension, flushing.

Dermatologic: Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculo-papular rash, urticaria.

Gastrointestinal: peptic ulceration, GI hemorrhage, GI perforation (see **Boxed WARNING, WARNINGS**), melena, acute pancreatitis.

Hemic and Lymphatic: postoperative 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, nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome.

OVERDOSAGE: In controlled overdosage, daily doses of 360 mg of ketorolac tromethamine injection given for five days (3 times the highest recommended dose), caused abdominal pain and peptic ulcers which healed after discontinuation of dosing. Metabolic acidosis has been reported following intentional overdosage.

Dialysis does not significantly clear ketorolac tromethamine from the blood stream.

DOSAGE AND ADMINISTRATION: THE COMBINED DURATION OF USE OF KETOROLAC TROMETHAMINE INJECTION AND KETOROLAC TROMETHAMINE TABLETS IS NOT TO EXCEED FIVE (5) DAYS. THE USE OF KETOROLAC TROMETHAMINE TABLETS IS ONLY INDICATED AS CONTINUATION THERAPY TO KETOROLAC TROMETHAMINE INJECTION.

Ketorolac tromethamine injection 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.

Ketorolac Tromethamine Tablets are indicated ONLY as continuation therapy to ketorolac tromethamine injection for the management of moderately severe, acute pain that requires analgesia at the opioid level. See also **PRECAUTIONS: Information for Patients.**

Transition from Ketorolac Tromethamine Injection to Ketorolac Tromethamine Tablets: The recommended dose for ketorolac tromethamine tablets is as follows:

Patients <65 years of age: Two (2) tablets as a first oral dose for patients who received **60 mg IM single dose, 30 mg IV single dose** or **30 mg multiple dose** ketorolac tromethamine injection followed by one (1) tablet of ketorolac tromethamine orally every 4 to 6 hours, not to exceed 40 mg/24 hr of ketorolac tromethamine tablets.

Patients ≥65 years of age renally impaired and/or less than 50 kg (110 lbs) of body weight: One (1) tablet as a first oral dose for patients who received **30 mg IM single dose, 15 mg IV single dose** or **15 mg multiple dose** ketorolac tromethamine injection followed by one (1) tablet of ketorolac tromethamine orally every 4 to 6 hours, not to exceed 40 mg/24 hr of ketorolac tromethamine tablets.

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

The maximum combined duration of use (parenteral and oral ketorolac tromethamine) is limited to 5 days.

HOW SUPPLIED: Ketorolac Tromethamine Tablets, USP:

10 mg - White, round, biconvex, unscored, film coated tablets, imprinted in black ink "SL" on one side and "608" on the other side in bottles of 100, 500 and 1000.

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

Store at controlled room temperature 15° - 30°C (59° - 86° F), protected from light and excessive humidity.

Rx only.

Manufactured by:
SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

WARNING

Ketorolac tromethamine tablets, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days) 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 intra-operatively 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 (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).

LABOR, DELIVERY AND NURSING

- The use of ketorolac tromethamine in labor and delivery is CONTRAINDICATED because it may adversely affect fetal circulation and the uterus.
- The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the possible 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

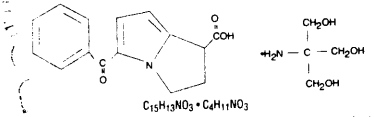
KETOROLAC TROMETHAMINE TABLETS

- Ketorolac tromethamine tablets are indicated only as continuation therapy to ketorolac tromethamine injection, and the combined duration of use of ketorolac tromethamine injection 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** and **Transition from Ketorolac Tromethamine Injection to Ketorolac Tromethamine Tablets**).

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**).

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, and the structural formula is:



$C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$

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 0.28. The molecular weight of ketorolac tromethamine is 376.41.

Each tablet for oral administration contains 10 mg ketorolac tromethamine. In addition, each tablet contains the following inactive ingredients: carnauba wax, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, synthetic black iron oxide and titanium dioxide.

CLINICAL PHARMACOLOGY: Pharmacodynamics: Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID). 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.

Pain relief was statistically different after ketorolac tromethamine dosing from that of placebo at 1/2 hour (the first time point at which it was measured) following the largest recommended doses of ketorolac tromethamine, and by 1 hour following the smallest recommended doses. The peak analgesic effect occurred within 2 to 3 hours and was 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. The extent of bioavailability following administration of the oral and IM forms of ketorolac tromethamine was equal to that following an IV bolus.

Linear Kinetics: 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.

Binding and Distribution: The ketorolac tromethamine racemate has been shown to be highly protein-bound (99%). Nevertheless, even plasma concentrations as high as 10 mcg/mL will only occupy approximately 5% of the albumin binding sites. Thus, the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations.

The mean apparent volume (Vβ) of ketorolac tromethamine following complete distribution was approximately 13 liters. This parameter was determined from single-dose data.

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.

Clearance and Excretion: 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.

The half-life of the 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 mcg/mL (SD ± 0.13) on Day 1 and 0.55 mcg/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 (elderly patients, renal failure patients, or hepatic disease patients).

Effect of Food: Oral administration of ketorolac tromethamine after a high fat meal resulted in decreased peak and delayed time-to-peak concentrations of ketorolac tromethamine by about 1 hour. Antacids did not affect the extent of absorption.

Kinetics in Special Populations: *Elderly 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 mcg/mL ± 0.77; young, 2.99 mcg/mL ± 1.03) (see **PRECAUTIONS: Use in the Elderly**).

P08-0608

KETOROLAC TROMETHAMINE TABLETS, USP

Rev. 6/98

Renally Impaired Patients: 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**).

Hepatic Effects: 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**).

TABLE 1
Table of Approximate 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] (mcg/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} (mcg/mL) [steady state q.i.d.]	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] (mcg/mL) [steady state q.i.d.]	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] (mcg/mL) [steady state q.i.d.]	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 feces = 6
% Dose excreted in urine = 91 % Plasma protein binding = 99
†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
††Not applicable because 60 mg is only recommended as a single-dose
**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.
[1]Time-to-peak plasma concentration
[2]Peak plasma concentration
[3]Trough plasma concentration
[4]Average plasma concentration
[5]Volume of Distribution

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])

Types 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 (3.4018.9)
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 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.

Clinical Studies: 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 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 tromethamine-IM 30 mg 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 tromethamine-IM 30 mg 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 perioperative morphine was allowed, ketorolac tromethamine-IV 30 mg, 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 tromethamine-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.

Clinical Studies with Concomitant Use of Opioids: 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 tromethamine-IV 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 tromethamine-IV plus PCA morphine as compared to patients receiving PCA-administered morphine alone.

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 (G.I.) bleeding was dose-dependent (see Table 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 G.I. Bleeding as Related to Age, Total Daily Dose, and History of G.I. Perforation, Ulcer, Bleeding (PUB) after up to 5 Days of Treatment with Ketorolac Tromethamine Injection

A. Patients without History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine injection			
	<60 mg	> 60 to 90 mg	> 90 to120 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. Patients with History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine injection			
	<60 mg	> 60 to 90 mg	> 90 to120 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: 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. 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.

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 musculature, thus increasing the risk of uterine hemorrhage.

The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the possible 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 intraoperatively 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.

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 days. The most serious risks associated with ketorolac tromethamine are

Gastrointestinal Ulcerations, Bleeding and Perforation: Ketorolac tromethamine is contraindicated in patients with previously documented peptic ulcers and/or G.I. 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 G.I. 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 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 B).

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. **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.

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 (e.g., 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 - 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 tromethamine-IM (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 perioperative use of ketorolac tromethamine injection. Therefore, perioperative use of ketorolac tromethamine should be avoided and postoperative use be undertaken with caution when hemostasis is critical (see **WARNINGS** and **PRECAUTIONS**).

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 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.

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

The *in vitro* binding of ***warfarin*** to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control versus 99.3%) when ketorolac plasma concentrations reach 5 to 10 mcg/mL. Ketorolac does not alter ***digoxin*** protein binding. *In vitro* studies indicate that, at therapeutic concentrations of ***salicylate*** (300 mcg/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 volunteers, ketorolac tromethamine tablets were co-administered with a single-dose of 25 mg ***warfarin***, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, ketorolac tromethamine injection was given with two doses of 5000 U of ***heparin*** to 11 healthy volunteers, resulting in a mean template

Mago

NDC 50111-608-01

Ketorolac Tromethamine Tablets, USP

10 mg

Oral tablets to be used only as a continuation therapy to ketorolac tromethamine injection.

Rx only

100 Tablets

Sidmak. LABORATORIES, INC.

EACH TABLET CONTAINS:
Ketorolac Tromethamine, USP ..... 10 mg

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

Store at controlled room temperature 15°-30°C (59°-86°F), protected from light and excessive humidity.

USUAL DOSAGE: See package insert.

Control No.:
Exp. Date:

Rev. 6/98

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

N 3 50111-608-01 6

NDC 50111-608-02

Ketorolac Tromethamine Tablets, USP

10 mg

Oral tablets to be used only as a continuation therapy to ketorolac tromethamine injection.

Rx only

500 Tablets

Sidmak. LABORATORIES, INC.

EACH TABLET CONTAINS:
Ketorolac Tromethamine, USP.... 10 mg

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

Store at controlled room temperature 15°-30°C (59°-86°F), protected from light and excessive humidity.

USUAL DOSAGE: See package insert.

Control No.:
Exp. Date:

Rev. 6/98

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

N 3 50111-608-02 3

NDC 50111-608-03

Ketorolac Tromethamine Tablets, USP

10 mg

Oral tablets to be used only as a continuation therapy to ketorolac tromethamine injection.

Rx only

1000 Tablets

Sidmak® LABORATORIES, INC.

EACH TABLET CONTAINS:
Ketorolac Tromethamine, USP..... 10 mg

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

Store at controlled room temperature 15°-30°C (59°-86°F), protected from light and excessive humidity.

USUAL DOSAGE: See package insert.

N 3 50111-608-03 0

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

Control No.:
Exp. Date:

Rev. 6/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-284

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO**: No. 1

2. **ANDA**: 75-284 [**Ketorolac Tromethamine Tablets USP, 10 mg**]

3. **NAME AND ADDRESS OF APPLICANT**:
Sidmak Laboratories, Inc.
Attention: Jairaj U. Mehta
17 West Street, P.O. Box 371,
East Hanover, NJ 07936

APPEARS THIS WAY
ON ORIGINAL

4. **LEGAL BASIS for ANDA SUBMISSION**:
Patent expired and no protected exclusivity exists.
Toradol®, 10 mg (Syntex Labs) [Patent expired May 16, 1997]

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: N/A

7. **NONPROPRIETARY NAME**:Ketorolac Tromethamine Tablets USP,10 mg

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

9. **AMENDMENTS AND OTHER DATES**:

Sidmak:

12/23/97	Submission of ANDA (received on 12/24/97)
01/26/98	Re: submission of documents with original signature

FDA:

02/03/98	Acknowledgment letter.

10. **PHARMACOLOGICAL CATEGORY**: Nonsteroidal anti-inflammatory.

11. **HOW DISPENSED**: Rx

12. **RELATED IND/NDA/DMF(s)**:
See Item 37 for a complete list of DMFs.
Innovator: Toradol®, 10 mg (Syntex Labs)

OGD has approved the following ANDAs for Ketorolac Tromethamine Tablets USP, 10 mg as of this review:

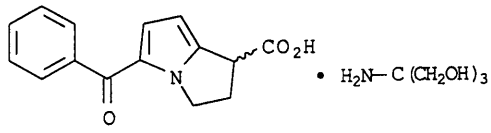
ANDA #	Applicant	Approval Date	Chemist
74-955	Chelsea	09/19/97	J. Smith
74-790	Roxane	06/26/97	J. Smith
74-761	Mylan	05/16/97	M. Maust
74-754	Teva	05/16/97	J. Smith

13. **DOSAGE FORM:** Oral Tablets

14. **Strength:** 10 mg

15. **CHEMICAL NAMES AND STRUCTURE:**

(±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)



$C_{15}H_{13}NO_3 . C_4H_{11}NO_3$

M.W.=376.41 CAS [*74103-07-4*]

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (MAJOR AMENDMENT)

19. **REVIEWER:**
Shing H. Liu, Ph.D.

DATE COMPLETED:
04/30/98
Revised 05/11/98 /S/ 05/11/98

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Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO**: No. 2

2. **ANDA**: 75-284 [Ketorolac Tromethamine Tablets USP, 10 mg]

3. **NAME AND ADDRESS OF APPLICANT**:
Sidmak Laboratories, Inc.
Attention: Jairaj U. Mehta
17 West Street, P.O. Box 371, East Hanover, NJ 07936

4. **LEGAL BASIS for ANDA SUBMISSION**: See CR #1

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: N/A

7. **NONPROPRIETARY NAME**:Ketorolac Tromethamine Tablets USP,10 mg

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

9. **AMENDMENTS AND OTHER DATES**:

Sidmak:

12/23/97	Submission of ANDA (received on 12/24/97)
01/26/98	Re: submission of documents with original signature
08/14/98	*Response to NA (MAJOR)

FDA:

02/03/98	Acknowledgment letter
05/27/98	NA (MAJOR) (faxed on 05/29/98) (based on CR #1)

10. **PHARMACOLOGICAL CATEGORY**: Nonsteroidal anti-inflammatory.

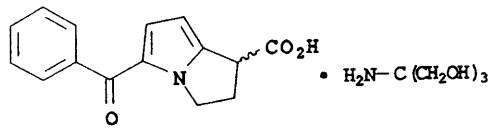
11. **HOW DISPENSED**: Rx

12. **RELATED IND/NDA/DMF(s)**: See CR #1

13. **DOSAGE FORM**: Oral Tablets

14. **Strength**: 10 mg

15. **CHEMICAL NAMES AND STRUCTURE**:
(±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)
$C_{15}H_{13}NO_3.C_4H_{11}NO_3$(
M.W.=376.41 CAS:[*74103-07-4*]



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (MINOR AMENDMENT due to DMF deficiency).

19. **REVIEWER:** Shing H. Liu, Ph.D.

DATE COMPLETED: 12/10/98

APPEARS THIS WAY
ON ORIGINAL

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Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO**: No. 3

2. **ANDA**: 75-284 [**Ketorolac Tromethamine Tablets USP, 10 mg**]

3. **NAME AND ADDRESS OF APPLICANT**:
Sidmak Laboratories, Inc.
Attention: Jairaj U. Mehta
17 West Street, P.O. Box 371, East Hanover, NJ 07936

4. **LEGAL BASIS for ANDA SUBMISSION**: See CR #1

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: N/A

7. **NONPROPRIETARY NAME**:Ketorolac Tromethamine Tablets USP,10 mg

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

9. **AMENDMENTS AND OTHER DATES**:

Sidmak:

12/23/97	Submission of ANDA (received on 12/24/97)
01/26/98	Re: submission of documents with original signature
08/14/98	Response to NA (MAJOR)
03/15/99	*Response to NA (MINOR)
05/28/99	*Telephone Amendment

FDA:

02/03/98	Acknowledgment letter
05/27/98	NA (MAJOR) (faxed on 05/29/98) (based on CR #1)
02/02/99	NA (MINOR) (faxed on 02/02/99) (based on CR #2)
05/14/99	Requested Telephone amendment

10. **PHARMACOLOGICAL CATEGORY**: Nonsteroidal anti-inflammatory.

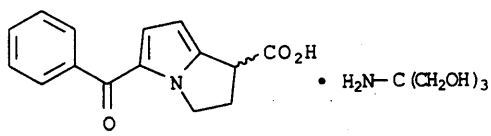
11. **HOW DISPENSED**: Rx

12. **RELATED IND/NDA/DMF(s)**: See CR #1

13. **DOSAGE FORM**: Oral Tablets

14. **Strength**: 10 mg

15. **CHEMICAL NAMES AND STRUCTURE**:
(±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)
$C_{15}H_{13}NO_3 . C_4H_{11}NO_3$
M.W.=376.41 CAS:[*74103-07-4*]



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

a

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Approvable.

19. **REVIEWER**:
Shing H. Liu, Ph.D.

DATE COMPLETED:
05/28/99

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-284

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-284 APPLICANT: Sidmak Laboratories

DRUG PRODUCT: Ketorolac tromethamine 10 mg tablet

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23, Suppl. 5.

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,

/S/

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

Ketorolac tromethamine
10 mg tablet
NDA #75-284
Reviewer: J. Lee
75284SA.O98

Sidmak Laboratories, Inc.
East Hanover, New Jersey
Submission date:
June 9, 1998
October 9, 1998

Review of a Study Amendment

This submission responds to the deficiencies in the review of the bio-studies in the original submission (sub. 12/23/97).

Fasted and fed studies:

1. Global means (at each concentration), percent CV, etc. were not calculated for quality control sample data. The sponsor was requested to tabulate and submit such data.

QC Controls - fasted

QC Value	Mean	%CV
[redacted] (n=31)	32.1	10.1
[redacted] (n=47)	306	6.2
[redacted] (n=48)	4988	5.1
[redacted] (n=48)	7601	5.9

QC Controls - fed

QC Value	Mean	%CV
[redacted] (n=43)	34.7	8.6
[redacted] (n=53)	282	6.4
[redacted] (n=53)	4981	5.4
[redacted] (n=53)	7549	5.3

2. The sponsor was asked to provide regression statistics for each subject in the calculation

of AUC_{inf}. The time points used in the regression were also asked to be supplied.

☞The sponsor has complied with the request.

3. No raw data was provided in the study reports except for those contained in the submitted chromatograms. The laboratory was asked to submit <u>all raw data</u> (peak height data for drug and IS, retention times, etc) for the analytical runs including those for the clinical samples, quality control samples, calibration standards and reassayed samples.

☞The sponsor has supplied the missing raw data.

4. The sponsor was requested to provide a table of mean drug levels with respect to treatment and sampling time.

☞The requested information was submitted (see attachments).

5. The sponsor was asked to explain the meaning/relevance of the data on pages 115-6 (fasted) and pages 82-3 (fed) of the statistical section.

☞The information was explained as a summary of the statistical analysis in table format, the values of which were used in generating the final statistical results.

6. The internal standard used in the assays was identified as warfarin (USP).

7. The information on the data diskettes were reformatted to be readable and resubmitted.

Fed study only:

8. It was noted that a number of subjects reached C_{max} at the first sampling time interval. The sponsor was asked to delete those C_{max} values and recompute the affected C_{max} averages and statistics. The sponsor did so and the revised information is presented below. [Note that 1st C_{max} occurrences involved only values in the <u>fasted</u> portion of the study]

	<u>Original</u> C_{max}	<u>Revised</u> C_{max}
Trt A	1327.29 ng/ml (n=17)	1284.17 ng/ml (n=12)
fed/fasted	0.60	0.62

9. The summary of statistical analysis [Table 4, Test (fed) vs Ref (fed)] contained PK values which did not correspond to the values generated by the SAS output for LS mean values. The sponsor was asked to explain this discrepancy and to revise and resubmit Table 4.

☞The discrepancy was satisfactorily explained and the table revised.

Comment:

1. All deficiencies have been satisfactorily addressed.

Recommendation:

1. The bioequivalence studies (fasted & fed) conducted by [redacted] for Sidmak Laboratories, Inc. on ketorolac tromethamine 10 mg tablet are acceptable. Sidmak's ketorolac tromethamine 10 mg tablet is deemed bioequivalent to Toradol® 10 mg tablet manufactured by Roche Laboratories.

2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 600 ml of water @ 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

   Not less than — , of the labeled amount of the drug in the tablet is dissolved in 45 minutes.

3. All bioequivalence requirements have been met.

/S/ 10/22/98
J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

/S/ 10/23/1998

Concur: /S/ Date: 10/27/98

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/10-22-98

cc: NDA #75-284 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

Table

Ketorolac Tromethamine 10 mg Tablets
P97-308
Mean Plasma Concentrations at Each Time Point

Time (hr)	A:TEST (mean)	Standard Deviation	%CV
0.00	0.0000	0.0000	.
0.08	79.5144	101.6438	127.83%
0.17	482.3975	378.9320	78.55%
0.25	889.9657	479.8244	53.91%
0.33	1120.8797	472.4007	42.15%
0.50	1246.4332	312.4287	25.07%
0.75	1214.2257	284.6276	23.44%
1.00	1082.5771	239.0402	22.08%
1.25	964.2053	222.9933	23.13%
1.50	861.4046	168.0612	19.51%
1.75	801.3120	174.5303	21.78%
2.00	732.8661	167.3451	22.83%
3.00	589.0360	183.2219	31.11%
4.00	462.2023	144.3482	31.23%
6.00	287.4406	84.7846	29.50%
8.00	171.4020	51.2617	29.91%
10.00	118.1320	37.0575	31.37%
12.00	90.3233	31.7225	35.12%
16.00	45.0301	27.1988	60.40%
24.00	13.2452	17.8199	134.54%
36.00	3.2493	8.7437	269.10%

Time (hr)	B:REFERENCE (mean)	Standard Deviation	%CV
0.00	0.0000	0.0000	.
0.08	16.9800	28.1365	165.70%
0.17	147.0551	179.3384	121.95%
0.25	451.1114	407.0693	90.24%
0.33	805.4171	548.3089	68.08%
0.50	1207.9259	476.4482	39.44%
0.75	1223.2927	312.3084	25.53%
1.00	1101.1193	291.4784	26.47%
1.25	982.4436	241.8297	24.62%
1.50	922.6123	257.8127	27.94%
1.75	838.2992	218.3114	26.04%
2.00	822.0351	270.6159	32.92%
3.00	637.6677	208.4508	32.69%
4.00	473.3605	164.6544	34.78%
6.00	284.8468	89.8793	31.55%
8.00	172.4306	64.3447	37.32%
10.00	125.6252	47.5920	37.88%
12.00	96.3317	42.8984	44.53%
16.00	51.1770	27.3112	53.37%
24.00	15.2215	17.5055	115.00%
36.00	3.1350	10.2229	326.09%

Pharmcokinetic Summary (fasted)

Trt A (test)

Variable	N	Mean	Std Dev	CV	T/R
TMAX	32	0.6209	0.3481	56.1	
CMAX	32	1425.76	344.50	24.2	0.98
AUCT	32	5195.81	1229.7	23.7	0.98
AUCINF	32	5544.73	1251.53	22.6	0.99
KE	32	0.132	0.056	42.0	
HL	32	6.289	2.810	44.7	
LCMAX	32	7.232	0.260	3.6	
LAUCT	32	8.531	0.222	2.6	
LAUCINF	32	8.597	0.216	2.5	

Trt B (ref)

Variable	N	Mean	Std Dev	CV
TMAX	32	0.8294	0.5790	69.8
CMAX	32	1452.29	293.57	20.2
AUCT	32	5319.15	1466.6	27.6
AUCINF	32	5625.97	1510.91	26.9
KE	32	0.1357	0.053	38.8
HL	32	6.041	2.826	46.8
LCMAX	32	7.260	0.208	2.9
LAUCT	32	8.545	0.264	3.1
LAUCINF	32	8.603	0.257	3.0

Table

Ketorolac Tromethamine 10 mg Tablets
P97-309
Mean Plasma Concentrations at Each Time Point

Time (hr)	A:TEST-FAST (mean)	Standard Deviation	%CV
0.00	0.0000	0.0000	.
0.25	1069.2493	512.1069	47.89%
0.50	1220.3350	322.0122	26.39%
0.75	1142.7668	238.3065	20.85%
1.00	977.7237	172.0285	17.59%
1.16	927.7208	165.8217	17.87%
1.33	849.5368	140.5328	16.54%
1.50	820.0061	135.1039	16.48%
1.66	763.8099	137.2335	17.97%
1.83	702.0435	167.0718	23.80%
2.00	655.5576	85.3356	13.02%
3.00	506.0026	100.9407	19.95%
4.00	387.9647	81.0174	20.88%
6.00	246.0091	48.9722	19.91%
8.00	153.8110	46.0150	29.92%
10.00	110.1918	39.4666	35.82%
12.00	83.0215	32.5058	39.15%
16.00	48.7606	28.0811	57.59%
24.00	19.2164	17.1705	89.35%
36.00	2.5540	7.2291	283.05%

Time (hr)	B:TEST-FED (mean)	Standard Deviation	%CV
0.00	0.0000	0.0000	.
0.08	212.7605	210.9300	99.14%
0.17	439.0770	298.9645	68.09%
0.25	597.1792	327.9861	54.92%
0.33	633.9865	314.9455	49.68%
0.50	669.4235	285.8345	42.70%
0.75	644.5081	236.9222	36.76%
1.00	672.0452	207.9676	30.95%
1.25	663.5074	190.9863	28.78%
1.50	676.8742	133.2536	19.69%
1.75	608.2265	133.0660	21.88%
2.00	551.3457	63.6430	11.54%
3.00	468.3309	68.1463	14.55%
4.00	315.2363	41.7609	13.25%
6.00	183.4064	38.4413	20.96%
8.00	126.5700	36.2770	28.66%
10.00	92.0558	32.4756	35.28%
12.00	49.1228	28.4463	57.91%
16.00	20.2747	17.0076	83.89%
24.00	5.4701	12.4569	227.73%

Time (hr)	C:REFERENCE (mean)	Standard Deviation	%CV
0.00	0.0000	0.0000	.
0.08	68.8047	75.5762	109.84%
0.17	327.7919	396.3953	120.93%
0.25	459.3169	374.5929	81.55%
0.33	526.0757	300.0073	57.03%
0.50	585.5111	273.2723	46.67%
0.75	613.4807	228.9825	37.33%
1.00	635.8564	229.3857	36.08%
1.25	663.3135	191.3909	28.85%
1.50	660.0879	172.3066	26.10%
1.75	645.3299	130.6210	20.24%
2.00	586.6870	108.2211	18.45%
3.00	465.8079	89.3628	19.18%
4.00	306.1326	61.9177	20.23%
6.00	165.5494	44.3109	26.77%
8.00	117.4529	36.7563	31.29%
10.00	86.7054	32.5246	37.51%
12.00	45.3518	23.2704	51.31%
16.00	12.5431	17.0524	135.95%
24.00	3.3096	10.5746	319.51%

Pharmacokinetic Summary (fed)

Trt A (test-fasted)

Variable	N	Mean	Std Dev	CV	B/A
TMAX	17	0.4559	0.1590	34.87	
CMAX	17	1284.17	345.52	26.03	0.62
AUCT	17	4861.25	1048.25	21.56	0.93
AUCINF	17	5081.76	1128.58	22.21	0.95
KE	17	0.145	0.08	57.72	
HL	17	5.791	2.25	38.82	
LCMAX	17	7.159	0.26	3.70	
LAUCT	17	8.466	0.22	2.65	
LAUCINF	17	8.509	0.23	2.68	

Trt B (test-fed)

Variable	N	Mean	Std Dev	CV	B/C
TMAX	17	1.4812	0.596	40.27	
CMAX	17	795.65	214.10	26.91	0.95
AUCT	17	4544.6	1004.28	22.10	1.07
AUCINF	17	4832.1	1116.09	23.10	1.07
KE	17	0.133	0.059	44.58	
HL	17	6.689	4.633	69.26	
LCMAX	17	6.647	0.258	3.89	
LAUCT	17	8.398	0.225	2.67	
LAUCINF	17	8.457	0.236	2.79	

Trt C (ref-fed)

Variable	N	Mean	Std Dev	CV
TMAX	17	1.849	0.777	42.02
CMAX	17	836.56	257.45	30.77
AUCT	17	4240.14	924.88	21.81
AUCINF	17	4498.19	1050	23.34
KE	17	0.150	0.061	40.63
HL	17	5.445	2.485	45.63
LCMAX	17	6.693	0.266	3.97
LAUCT	17	8.331	0.210	2.53
LAUCINF	17	8.388	0.220	2.63

CC: ANDA 75-284
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Nerurkar /S/ for BioSign Off List
HFD-655/ J. Lee 10/22/98 /S/ 10/23/98
BIO DRUG FILE

Printed in Final on /S/ 10/27/98
X:\NEW\FIRMSnz\Sidmak\ltrs&rev\75284SA.O98

BIOEQUIVALENCY - ACCEPTABLE

5. STUDY AMENDMENT (STA) 6/9/98 Strengths: 10 mg
Outcome: AC

5. STUDY AMENDMENT (STA) 10/9/98 Strengths: 10 mg
Outcome: AC

OUTCOME DECISIONS:
AC - Acceptable NC - No Action

WINBIO COMMENTS:
Deficiencies are satisfactory. Bio-studies now acceptable.

APPEARS THIS WAY
ON ORIGINAL

Ketorolac tromethamine
10 mg tablet
NDA #75-284
Reviewer: J. Lee
75284SD.D97

Sidmak Laboratories, Inc.
East Hanover, New Jersey
Submission date:
December 23, 1997

Review of Fasting and Fed in-vivo Bioavailability Studies and Dissolution Testing Data

Objective:

To determine the relative bioavailability of 10 mg ketorolac tromethamine tablets after administration of single doses to healthy male subjects under both fasted and fed conditions.

Fasting Study

Study Design:

The clinical study (#P97-308) was conducted at [redacted]
under the supervision of [redacted]

Thirty-two male volunteers between the ages of 18-45 years and within 10% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination and clinical laboratory tests [hematology, serum chemistry and urinalysis].

Those with any of the following conditions were excluded:

History or presence of:

- clinically significant cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine or neurologic disorders; or psychiatric disease
- alcohol or drug abuse
- positive hepatitis B surface antigen screen or a reactive HIV antibody screen
- allergic response to ketorolac tromethamine or related drugs
- use of tobacco products

Rx and OTC medications were not allowed within 14 and 7 days, respectively, of the first drug

administration. There was to be no alcohol or caffeine consumption at least 48 hours prior to drug administration.

The study was designed as a randomized, two-way crossover study with a 7 day washout period between dosings. Treatments consisted of a single 20 mg (2 x 10 mg) dose of the following:

A. Ketorolac tromethamine
10 mg tablet, batch #96-006T
Sidmak Laboratories, Inc.
Mnfg. date: May, 1996

B. Toradol®
10 mg tablet, batch #B2484
Roche Laboratories [mnfg'd by Syntex Puerto Rico for Roche Laboratories]
expiry date: May, 1999

Thirty-two subjects were dosed according to the following regimen:

	Period I 11/01/97	Period II 11/08/97
sequence I	A	B
sequence II	B	A

sequence I - subj. # 2, 4, 8, 10, 11, 16, 17, 20, 22, 23, 25, 26, 27, 28, 30, 31

sequence II - subj. #1, 3, 5, 6, 7, 9, 12, 13, 14, 15, 18, 19, 21, 24, 29, 32

All subjects completed the study.

After an overnight fast, subjects were given a 20 mg dose (2 x 10 mg) of ketorolac tromethamine with 240 ml of water. Fasting continued for 4 hours post-dose. Blood samples (10 ml) were

All sampling deviations are noted on page 20 of the clinical report. Most deviations were within a couple of minutes of the scheduled sampling time and are deemed insignificant.

Twelve subjects reported experiencing a total of 16 adverse events, only one of which (abdominal pain, subj. #31, ref.) was judged to have been probably related to the study medication. None were considered serious. The adverse events summary is attached.

There were a number of deviations from protocol reported, centering around self-medication with OTC products. The clinical investigators judged that the self-medications should not compromise the outcome or validity of the study.

Redacted 1

pages of trade secret and/or confidential commercial information

Data Analysis:

Plasma data was analyzed by an analysis of variance procedure (SAS, version 6.12) to determine statistically significant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters. All thirty-two subjects completed the crossover; thirty-two datasets were analyzed.

Results:

No statistically significant differences were found in any of the pharmacokinetic indices, neither on the original nor on the ln-transformed scale. No sequence effects were observed either. There was a ≤2.8% difference between the test and reference formulations for plasma levels of ketorolac in AUC_{0-t}, AUC_{inf} and C_{max}. The 90% shortest confidence intervals for ketorolac, using least squares means, are presented below:

		90% CI
original scale	AUC_{0-t} (n=32)	[93.6; 101.8]
	AUC_{inf} (n=32)	[94.2; 102.9]
	C_{max} (n=32)	[89.5; 106.8]
ln-transformed scale	AUC_{0-t} (n=32)	[94.5; 102.9]
	AUC_{inf} (n=32)	[95.3; 103.9]
	C_{max} (n=32)	[88.5; 106.7]

Fed Study

Study Design:

The clinical and analytical facilities for this study were the same as that employed in the fasting study. The inclusion and exclusion criteria for subject selection were also the same.

The study (#P97-309) was a randomized, three treatment, three period, six sequence crossover. Treatments consisted of the same two batches of test and reference products (used in the fasting study). A seven day washout period separated the dosings.

Eighteen subjects were dosed according to the following regimen:

	period I 09/28/97	period II 10/05/97	period III 10/12/97
sequence I	A	B	C
sequence II	A	C	B
sequence III	B	A	C
sequence IV	B	C	A

sequence V	C	A	B
sequence VI	C	B	A

sequence I - subj #9, 10, 16
sequence II - subj #3, 4, 14
sequence III - subj #1, 17, 18
sequence IV - subj #2, 13, 15*
sequence V - subj #5, 6, 11
sequence VI - subj #7, 8, 12

Treatment A: 2 x 10 mg ketorolac tromethamine tablet (Sidmak) following an overnight fast
Treatment B: 2 x 10 mg ketorolac tromethamine tablet (Sidmak) following a standard breakfast*
Treatment C: 2 x 10 mg Toradol® tablet (Roche) following a standard breakfast*

*standard breakfast: 1 buttered English muffin
1 fried egg
1 slice of American cheese
1 slice of Canadian bacon
1 serving of hash brown potatoes
6 fl oz of orange juice
8 fl oz of whole milk

Of the 18 subjects enrolled in the study, one (subject #15) withdrew from the study before the second period dosing for personal reasons. Seventeen subjects completed all phases of the study.

After an overnight fast, subjects on treatment A were dosed. Those on treatment B or C were served a standard breakfast 30 minutes before dosing. Fasting continued for 4 hours post dose. Blood was drawn in vacutainers (containing EDTA) at 15, 30, 45, 60, 70, 80, 90, 100 and 110 minutes; and at 2, 3, 4, 6, 8, 10, 12, 16, 24 and 36 hours.

Deviations from the blood sampling schedule are noted on page 19 of the clinical report. They are deemed insignificant.

There were a total of 19 adverse events reported in 6 of 18 subjects, only several of which were possibly were judged possibly related to the study drug. None were considered serious.

Analytical:

The analytical method and validation was the same as that used in the fasting study.

The standard curve summary for this fed study showed a coefficient of determination (r^2) of $\geq$0.98504. The coefficient of variation for the standards ranged from 2.9% (at 10,000 ng/ml; n=18) to 11.2% (at 20 ng/ml; n=18). There were two rejected standard curve value in all the runs.

The precision of the assay was monitored by the quality control samples that were run in triplicate with each group of samples. This data was not summarized.

All stability and recovery data are the same as reported in the fasting study review.

Zero hour samples showed no quantifiable interference at the retention time of the drug peak.

Data Analysis and Results:

Means, standard deviations and CV%s were calculated for AUC_{0-t}, AUC_{inf}, C_{max}, t_{max}, kel, $t_{½}$ and concentrations at each sampling time point (see attached tables). Areas under the curve showed 7% difference for T/R (fed) and a 5% difference in C_{max} ratios. There was no food effect observed for T(fed)/T(fasted) in AUCs, but there was a decrease (40%) in C_{max} and a one hour delay in T_{max}. These effects of food (after high fat meal) were also noted in the labeling for Toradol®.

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using the current USP dissolution method. The resultant summaries are attached.

Content Uniformity:

The assay for content uniformity for 10 dosage units of the Sidmak product was 98.5% of label claim; range = 96.0% - 101.1% (1.6% CV); for Toradol, the C.U. was 99.1% of label claim - range = 97.7 - 100.8 (0.88% CV).

Batch Size:

The batch size for the bio-batch of Sidmak's 10 mg ketorolac tromethamine was —— dosage units.

Comment:

Fasted and fed studies:

1. Global means (at each concentration), percent CV, etc. were not calculated for quality control sample data. The sponsor should tabulate and submit such data.

2. The sponsor should provide regression statistics for each subject in the calculation of AUC_{inf}. The time points used in the regression should also be supplied.

3. No raw data was provided in the study reports except for those contained in the submitted chromatograms. The laboratory should submit all raw data (peak height data for drug and IS, retention times, etc) for the analytical runs including those for the clinical samples, quality control samples, calibration standards and reassayed samples. The raw data should be organized with respect to the samples in each run.

4. The sponsor is requested to provide a table of mean drug levels with respect to treatment and sampling time. The percent CV at each sampling time should be included.

5. The sponsor should explain the meaning/relevance of the data on pages 115-6 (fasted) and pages 82-3 (fed) of the statistical section.

6. The sponsor should identify the internal standard used in the assays.

7. The information on the data diskettes included with the application do not reflect the same values that are contained in the accompanying printouts [there are also missing (###) values]. The sponsor should resubmit the information in the data diskettes. Discrete data should be space delimited. All information in the diskettes should be arranged sequentially in a flat ascii text format.

Fed study only:

8. It is noted that subjects #3 (per I, trt A), #2 (per III, trt A), #7 (per III, trt A), #12 (per III, trt A) and #13 (per III, trt A) reached C_{max} at the first sampling time interval. The sponsor should delete those C_{max} values and recompute the affected C_{max} averages and statistics.

9. The summary of statistical analysis [Table 4, Test (fed) vs Ref (fed)] contain PK values which do not correspond to the values generated by the SAS output for LS mean values. The sponsor should explain this discrepancy.

   The sponsor is requested to revise and resubmit Table 4 to include data in the fasted leg of the study.

Recommendation:

1. The bioequivalence studies conducted by ———— for Sidmak Laboratories, Inc. on ketorolac tromethamine 10 mg tablet is incomplete per comments #1-9.

   Comments #1-9 should be forwarded to the sponsor.

/S/ 4/9/98

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

/S/ 4/13/98

Concur: /s/ Date: 4/27/98

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/04-09-98

cc: NDA #75-284 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

USP XXIII Apparatus II Basket _____ Paddle x rpm 50

Medium: water Volume: 600 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Toradol® 10 mg tablet

Assay Methodology: _____

Results

Time (min)	Test Product Lot # 96-006T Mean % Dissolved	Range	(CV)	Reference Product Lot # B2484 Mean % Dissolved	Range	(CV)
15	89		(6.6)	88		(17)
30	94		(5.0)	97		(6.0)
45	97		(4.0)	99		(4.3)
			( )			( )
			( )			( )
			( )			( )

	Lot #			Lot #		
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )

Ketorolac Tromethamine 10 mg Tablets
P97-308 (fasted)
Summary of Statistical Analysis

PK	LS MEAN			GEOMETRIC MEAN			Mean Square	Standard	90 % Confidence Interval			Power of
Variable	Test	Reference	Difference	Test	Reference	% Ratio	Error	Error	Lower Limit	Upper Limit	P-values	ANOVA
LAUC	8.5307	8.5446	-0.0139	5068.1544	5139.0217	98.6210	0.00993908	0.0249	94.54	102.88	0.5816	1.0000
$LAUC_{inf}$	8.5974	8.6025	-0.0051	5417.6260	5445.4463	99.4891	0.01048950	0.0256	95.26	103.91	0.8428	1.0000
LC_{max}	7.2316	7.2604	-0.0288	1382.4810	1422.8355	97.1638	0.04867314	0.0552	88.48	106.70	0.6057	0.9746

PK	LS MEAN				Standard	90 % Confidence Interval			Power of
Variable	Test	Reference	Difference	% Ratio	Error	Lower Limit	Upper Limit	P-values	ANOVA
AUC	5195.8056	5319.1491	-123.3435	97.6811	129.5052	93.55	101.81	0.3485	1.0000
AUC_{inf}	5544.7312	5625.9747	-81.2435	98.5559	143.3948	94.23	102.88	0.5752	1.0000
C_{max}	1425.7553	1452.2888	-26.5334	98.1730	74.1552	89.51	106.84	0.7230	0.9663
t_{max}	0.6209	0.8294	-0.2084	74.8681	0.1141			0.0777	0.2907
k_{elim}	0.1325	0.1357	-0.0032	97.6330	0.0116			0.7828	0.6232
$t_{1/2}$	6.2886	6.0405	0.2481	104.1067	0.7151			0.7311	0.3729

Sixteen adverse events were reported in twelve of thirty-two subjects dosed over the course of the study. The adverse events are summarized in the following table (detailed information in Attachment 6):

(fasted)

Event No.	Subject No.	Init.	Event	Relationship to Study Drug	Study Drug
01	31	MLB	Abdominal Pain (Stomach ache)	1	B
02	12	MDF	Bump on Arm (Left Arm Antecubital Space)	4	B
03	04	YGT	Coughing (Cough)	4	-
04	10	KJT	Dizziness (Dizziness)	4	A
05	16	JRJ	Headache	4	A
06	18	DJH	Headache	4	B
07	22	MGH	Headache	3	A
08	24	SMO	Headache	4	B
09	24	SMO	Headache	4	B
10	10	KJT	Nausea	4	A
11	23	MAC	Pharyngitis (Scratchy Throat)	4	A
12	20	AJM	Pharyngitis (Sore Throat)	4	A
13	28	MZO	Purpura (Hematoma Right Arm Antecubital Space)	4	B
14	17	BSD	Rhinitis (Stuffy Nose)	4	A
15	28	MZO	Rigors (Shivers)	3	B
16	18	DJH	Sore Arm (Right Arm Antecubital Space)	4	B

Legend: Relationship to Study Drug: 1 = Probable; 2 = Possible; 3 = Remote; 4 = Unrelated
Study Drug: A = Ketorolac Tromethamine Tablets [Sidmak Laboratories, Inc.]
B = Toradol® Tablets [Syntex Puerto Rico, Inc., Mfd. for Roche Laboratories, Inc.]
Clarification: The general description in parenthesis is at the request of the ~~~~ to avoid the occasional misleading terminology of WHO.

Of the sixteen reported adverse events, one was probably related to study drug. In the opinion of the investigators, the other fifteen adverse events were unrelated to study drug. None of the adverse events were considered serious or resulted in terminating any subject from study participation.

Overall, the clinical laboratory measurements (see Clinical Laboratory Evaluations in Attachment 7) were generally unremarkable over the course of the study. All screening clinical laboratory samples and requested repeat samples were collected and the results interpreted prior to Period I dose administration.

Ketorolac Tromethamine 10 mg Tablets
P97-309 (fed)
Summary of Statistical Analysis

PK Variable	LS MEAN Test(fed)	Reference(fed)	Difference	% Difference	% Ratio	Standard Error	P-values	Power of ANOVA
AUC	4545.6423	4242.9191	302.7232	7.1348	107.1348	187.2811	0.1171	0.9473
AUC_{inf}	4834.9352	4500.8377	334.0974	7.4230	107.4230	199.5698	0.1051	0.9455
C_{max}	793.3643	834.5484	-41.1841	4.9349	95.0651	72.7144	0.576	0.4421
t_{max}	1.4987	1.8502	-0.3515	18.9980	81.0020	0.1751	0.0542	0.3862
k_{elim}	0.1333	0.1493	-0.0160	10.7054	89.2946	0.0158	0.3221	0.3193
$t_{1/2}$	6.6984	5.4535	1.2449	22.8273	122.8273	0.9681	0.2091	0.1447

PK Variable	LS MEAN Test	Reference	Difference	GEOMETRIC MEAN Test	Reference	% Ratio	Standard Error	P-values	Power of ANOVA
LAUC	8.3990	8.3315	0.0675	4442.5730	4152.7830	106.9782	0.0432	0.1292	0.983132
$LAUC_{inf}$	8.4583	8.3882	0.0700	4713.8252	4394.9789	107.2548	0.0433	0.1166	0.982693
LC_{max}	6.6439	6.6911	-0.0472	768.0724	805.1841	95.3909	0.0671	0.4882	0.747554

The follo bjects reported concurrent problems and medication usage over the course of the study [T: lems are cross-referenced as adverse events on page 21.]:

Event No.	ct Subject Init.	Problem	Medication	Average Daily Dose	Study Day(s)
01	RJK	Threw Back Out	Ibuprofen (200 mg)	6 tabs	13
02	RJK	Threw Back Out	Ibuprofen (200 mg)	2 tabs	14
03	JMZ	Runny Nose, Headache, Sore Throat	Complete Allergy Relief (Diphenydramine Hydrochloride 25 mg)	2 tabs	11

In the opini f the clinical investigators, the reported medications should not compromise the outcome or dity of the study, and continued participation was allowed.

Nineteen adve events were reported in six of eighteen subjects dosed over the course of the study. The adv rse events are summarized in the following table (detailed information in Attachment 6):

(fed)

Event No.	Subject No.	Init.	Event	Relationship to Study Drug	Study Drug
01	15	SMC	Asthenia (Weak)	4	B
02	02	RJK	Back Pain (Threw Back Out)	4	C
03	15	SMC	Depersonalization (Feels Funny)	4	B
04	08	JMZ	Diarrhea	2	B
05	15	SMC	Dizziness (Dizzy)	4	B
06	07	JMF	Headache	2	A
07	08	JMZ	Headache	4	B
08	15	SMC	Headache	4	B
09	15	SMC	Nausea (Queasy Stomach)	4	B
10	15	SMC	Pallor (Pale)	4	B
11	15	SMC	Parestheisa (Ice Cold Arms)	4	B
12	15	SMC	Paresthesia (Ice Cold Hands)	4	B
13	08	JMZ	Pharyngitis (Sore Throat)	4	B
14	12	DKT	Pharyngitis (Sore Throat)	4	B
15	10	DAN	Rash (Rash Right Arm)	2	B
16	08	JMZ	Rhinitis (Runny Nose)	4	B
17	12	DKT	Rhinitis (Runny Nose)	4	B
18	07	JMF	Sprained Right Ankle	4	B
19	15	SMC	Tremor (Shaky)	4	B

Legend: Relationship to Study Drug: 1 = Probable; 2 = Possible; 3 = Remote; 4 = Unrelated
Study Drug: A (fasting) = Ketorolac Tromethamine Tablets [Sidmak Laboratories, Inc.]
B (fed) = Ketorolac Tromethamine Tablets [Sidmak Laboratories, Inc.]
C (fed) = Toradol® Tablets [Syntex Puerto Rico, Inc., Mfd. for Roche Laboratories, Inc.]
Clarification: The general description in parenthesis is at the request of the ——— to avoid the occasional misleading terminology of WHO.

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:75-284 APPLICANT: Sidmak Laboratories, Inc.

DRUG PRODUCT: Ketorolac tromethamine 10 mg tablet

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

Fasted and fed studies:

1. Global means (at each concentration), percent CV, etc. were not calculated for quality control sample data. Please tabulate and submit such data.

2. Please provide regression statistics for each subject in the calculation of AUC_{inf}. The time points used in the regression should also be supplied.

3. No raw data was provided in the study reports except for those contained in the submitted chromatograms. Submit all raw data (peak height data for drug and IS, retention times, etc) for the analytical runs including those for the clinical samples, quality control samples, calibration standards and reassayed samples. The raw data should be organized with respect to the samples in each run.

4. Please provide a table of mean drug levels with respect to treatment and sampling time. The percent CV at each sampling time should be included.

5. Explain the meaning/relevance of the data on pages 115-6 (fasted) and pages 82-3 (fed) of the statistical section.

6. Identify the internal standard used in the assays.

7. The information on the data diskettes included with the application do not reflect the same values that are contained in the accompanying printouts [there are also missing (###) values]. Please resubmit the information in the data diskettes. Discrete data should be space delimited. All information in the diskettes should be arranged sequentially in a flat ascii text format.

Fed study only:

8. It is noted that subjects #3 (per I, trt A), #2 (per III, trt A), #7 (per III, trt A), #12 (per III, trt A) and #13 (per III, trt A) reached C_{max} at the first sampling time interval. Please delete those C_{max} values and recompute the affected C_{max} averages and statistics.

9. The summary of statistical analysis [Table 4, Test (fed) vs Ref (fed)] contain PK values

which do not correspond to the values generated by the SAS output for LS mean values. Please explain this discrepancy.

Please revise and resubmit Table 4 to include data in the fasted leg of the study.

Sincerely yours,

/S/

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

CC: ANDA 75-284
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements:
HFD-655/ J. Lee /S/ 4/9/98
HFD-655/ SG Nerurkar /S/ 4/13/98
HFD-617/ Chamberlin
HFD-650/ Conner /S/ 4/27/98

Printed in draft on \ \
Printed in final on \ \
x:\new\firmsnz\Sidmak\ltrs&rev\75284SD.D97

BIOEQUIVALENCY - DEFICIENCIES

1. **FASTING STUDY** (STF) Strengths: 10 mg
Clinical:
Analytical: **Outcome:** IC

2. **FOOD STUDY** (STP) Strengths: 10 mg
Clinical:
Analytical: **Outcome:** IC

4. **DISSOLUTION DATA** (DIS) ~~All~~ Strengths 10 mg
Outcome: **AC** /S/

OUTCOME DECISIONS:
UN - Unacceptable (fatal flaw) **IC** - Incomplete

WINBIO COMMENTS:
Biostudies (fasted & fed) are incomplete due to analytical and statistical deficiencies.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-284

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY

ANDA: 75-284

DRUG PRODUCT: Ketorolac Tromethamine Tablets USP, 10 mg

FIRM: Sidmak Laboratories, Inc.

DOSAGE FORM: Oral Tablet

STRENGTH: 10 mg

cGMP STATEMENT/EIR UPDATE STATUS: EER.acceptable on 06/02/98

BIO STUDY: Acceptable (the bioequivalence reivew was signed off on 10/27/98). The recommended dissolution specifications and conditions are as follows:

The dissolution testing should be conducted in 600 mL of water, using apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:

> Not less than — of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

This is the USP 23 monograph specification.

Method VALIDATION: Not required (the drug product is listed in USP).

STABILITY: Sidmak submitted three months accelerated (40°C/75% RH) stability data of the executed ANDA batch packaged in 100s, 500s and 1000s in the proposed container/closure system. Sidmak has completed the full term room temperature stability study. All reported data are within specifications as listed. A 24 month expiration date is proposed.

Sidmak's proposed stability tests and specifications are as follows:

1. *Dissolution* (USP): 600 ml water, apparatus 2, 50 rpm for 45 minutes, NLT — (Q) of the labeled amount of ketorolac tromethamine is dissolved in 45 minutes
2. *Assay* (USP): 90.0-110.0% of the labeled amount
3. *Related Compounds* :
   — NMT —
   — NMT —
   Total Impurities: NMT —
4. *Description* : White, round, biconvex, film coated tablets, imprinted "SL" on one side and "608" on the other side in black ink.
5. — NMT —

LABELING: Labeling approval summary was signed off on 09/22/98.

STERILIZATION VALIDATION: (IF APPLICABLE): N/A

SIZE OF BIO Batch: — Tablets (Lot #96-006T). The source of the bulk drug substance was — (Holder of DMF # — . DMF # — was last reviewed on 05/14/99, and was found adequate.

SIZE OF STABILITY BATCHES: same as bio batch.

PROPOSED PRODUCTION BATCHES: — and — tablets

Review Chemist: /S/ **DATE:** 06/01/99
Shing H. Liu, Ph.D.

Team Leader: /S/ **DATE:** 6/3/99
Vilayat Sayeed, Ph.D.

CC: ANDA 75-284
Division File
V:\Firmsnz\sidmak\ltrs&rev\75284app.sum

RECORD OF TELEPHONE CONVERSATION

The Agency called Ms. Deborah Parkay to inform her that the policy had changed for [redacted] The Sponsor was requested to send a commitment to perform routine [redacted] testing on all batches. The Sponsor was also asked to commit to using the recommended mean specification of [redacted] with an RSD of not more than [redacted] The sample size must be 1-3 times the unit dose.

Post-approval, the Sponsor can discuss their process with the field and may request some relief from this commitment.

FDA participants:
Vilayat Sayeed-Chemistry Team Leader
Bonnie McNeal-Project Manager

Filename:
V:\FIRMSNZ\SIDMAK\TELECONS\75284.002.doc

DATE
May 14, 1999

APPLICATION NUMBER
75-284

IND NUMBER

TELECON

INITIATED BY
_ **APPLICANT/**

X **FDA**

PRODUCT NAME
Ketorolac Tromethamine Tablets USP, 10mg

FIRM NAME
Sidmark Laboratories, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Deborah Pakay

TELEPHONE NUMBER
(973) 599-4353

SIGNATURE

Bonnie McNeal

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

Fax Cover Sheet

DATE: May 28, 1999

TO: Ms. Bonnie McNeil, Office of Generic Drugs

FAX: 301-594-0180

FROM: Debbie Pakay, Manager, Regulatory Affairs

PHONE: (973) 599-4353 **FAX:** (973) 599-5721

RE: Telephone Amendment for ANDA No. 75-284
Ketorolac Tromethamine Tablets USP, 10 mg

Number of pages including cover sheet: 2

MESSAGE:

As per my conversation with you today, I am faxing you a copy of the commitment we are submitting today for the above mentioned ANDA.

Two hard copies of this commitment (telephone amendment) are being sent to the Document Control Room via Federal Express Overnight. You should receive them on Tuesday, 6/1/99.

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

ANDA Number: 75-284 Date of Submission: December 23, 1997

Applicant's Name: Sidmak Laboratories, Inc.

Established Name: Ketorolac Tromethamine Tablets USP, 10 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Please note that your drug product is now the subject of a USP monograph titled "Ketorolac Tromethamine Tablets". We encourage you to include "USP" in the established name of your drug product. We refer you to USP 23, supplement #1 for further guidance.

   b. Revise to replace the ' [redacted]." statement with "℞ only" on your labels and labeling. See Section 126 of the FDA Modernization Act of 1997.

2. CONTAINER - 100's, 500's, & 1000's

   a. See GENERAL COMMENTS.

   b. Revise the storage requirement to read as follows:

      Store at controlled room temperature 15° - 30°C (59° - 86°F), protected from light and excessive humidity.

   c. ... ketorolac tromethamine injection. [rather than [redacted]

3. INSERT

   a. GENERAL

      i. See GENERAL COMMENTS.

      ii. Replace ' [redacted] with "ketorolac tromethamine tablet" throughout the text.

      iii. Replace ' [redacted] with

"ketorolac tromethamine injection" throughout the text.

iv. Some of the information associated with ketorolac tromethamine injection should be included in the package insert labeling, considering that the oral regimen is employed as a continuation therapy for the parenteral administration of ketorolac tromethamine.

v. In order to assist you in making these changes, we have enclosed the latest approved insert labeling from Mylan Pharmaceuticals Inc. (approved May 16, 1997) for guidance. In addition, we have the following comments:

b. BOXED WARNING

The innovator utilizes bullets (■) preceding each WARNINGS statement. We encourage you to utilize a similar feature to draw attention to these important statements and render better readability to your label.

c. DESCRIPTION

i. We encourage the inclusion of the molecular weight.

ii. Last sentence - Revise to read as follows:

In addition, each tablet contains the following inactive ingredients: carnauba wax, ...

d. HOW SUPPLIED - Revise to read as follows:

i. ...,round, biconvex, unscored, film coated tablets, imprinted in black ink "SL" on one side and "608" on the other side in bottles ...

ii. Refer to comment (b) under CONTAINER.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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 the last submitted labeling with all differences annotated and explained.

/S1

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: A copy of the last approved package insert labeling from Mylan Pharmaceutical Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-284

CORRESPONDENCE

ANDA 76-346

APPEARS THIS WAY
ON ORIGINAL

MAY 15 2002

PLIVA USA Inc.
U.S. Agent for: PLIVA Pharmaceutical Industry, Inc.
Attention: Damir Nevjestic
150 East 58th Street
16th Floor
New York, N.Y. 10155

Dear Sir:

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

Reference is made to our "Refuse to Receive" letter dated March 11, 2002 and your amendment dated March 26, 2002.

NAME OF DRUG: Torsemide Tablets, 5 mg, 10 mg and 20 mg

DATE OF APPLICATION: December 31, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 27, 2002

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

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:

Tim Ames
Project Manager
(301) 827-5848

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

/S/

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

cc: ANDA 76-346
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

APPEARS THIS WAY
ON ORIGINAL

Endorsement: HFD-615/GDavis, Chief, PCB /S/ 15-MAY-2002 ____date
HFD-615/SMiddleton, CSO /S/ ____date 5/15/02
Word File
V:/FIRMSNZ/PLIVA/LTRS&REV/76346.ACK
FT/ StM 5/15/02
ANDA Acknowledgment Letter!

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

May 28, 1999

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

Re: Ketorolac Tromethamine Tablets USP, 10 mg, ANDA #75-284
Telephone Amendment to a Pending Application

Dear Sir/Madam:

Reference is made to the telephone conversation between the Office of Generic Drugs (Ms. Bonnie McNeil and Dr. Sayeed Vilayat) and Sidmak Laboratories, Inc. (Ms. Debbie Pakay) on May 14, 1999. During this conversation, Dr. Vilayat requested that Sidmak incorporate ——— testing for routine production.

Sidmak Laboratories, Inc. commits to perform ——— testing on all commercial production batches of this product. The specification of ——— (for the mean) with an RSD of NMT — will be instituted. The unit dose sample will be one to three times the unit dose size.

Should you have any questions or require any additional information, please do not hesitate to contact either Mr. Roger Schwede at (973) 599-4352 or myself at (973) 599-4353.

Sincerely,

Deborah L Pakay

Deborah L. Pakay
Manager, Regulatory Affairs

F:\worddata\andas\75284-6

4.1

Sidmak LABORATORIES, INC.

7 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

March 15, 1999

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

NDA ORIG AMENDMENT
N/A W

Re: Ketorolac Tromethamine Tablets USP, 10 mg, ANDA #75-284
Amendment to a Pending Application

Dear Sir/Madam:

Reference is made to the minor amendment letter (copy attached) faxed to Sidmak Laboratories, Inc. on February 2, 1999. This letter commented that ——, the holder of DMF # —— , has been notified of deficiencies in their drug master file.

We have received a copy of the letter from —— . to the agency dated March 5, 1999 (copy attached), which states that they have submitted the information requested. In turn, we are submitting our response to this minor amendment.

Thank you for your time and attention with this matter. Should you have any questions or require any additional information, please do not hesitate to contact either Mr. Roger Schwede at (973) 599-4352 or myself at (973) 599-4353.

Sincerely,

Deborah L Pakay

Deborah L. Pakay
Manager, Regulatory Affairs

F:\worddata\andas\75284-5

RECEIVED
MAR 16 1999
GENERIC DRUGS

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (973) 386-5566 ● (800) 922-0547

August 14, 1998

NDA ORIG AMENDMENT
N-AC

RECEIVED
AUG 17 1998
GENERIC DRUGS

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

Re: Ketorolac Tromethamine Tablets USP, 10 mg, ANDA #75-284
RESPONSE TO A MAJOR AMENDMENT

Dear Sir/Madam:

Reference is made to the Office of Generic Drugs letter dated 5/27/98, faxed to Sidmak Laboratories on 5/29/98 (copy attached). This letter provided deficiencies pertaining to the abbreviated new drug application submitted on 12/23/97.

The following represents Sidmak's response to the agency's comments. For your convenience, the comment is copied as it appeared on the letter and has been italicized. Sidmak's response is printed underneath the comment for each item.

A. Deficiencies

1. Please be advised that Drug Master File (DMF) No. ——— for Ketorolac Tromethamine was reviewed, and was found deficient. The holder of the DMF, ——— has been notified of the deficiencies.

We have contacted the U.S. agent for ——— regarding the deficiencies in DMF No. ——— It is our understanding that ——— will submit their response by Sept. 15, 1998.

2. [redacted]

Redacted 3

pages of trade secret and/or confidential commercial information

6. *Please add cautionary notes in Method FP-608-01 regarding protection of sample solution and standard solution from light.*

A cautionary note is included at the beginning of Method FP-608-03 (for the finished product) and Method ST-608-02 (for stability) regarding the protection of solutions from light.

C. *Review of Professional Labeling*

1. The general comments regarding the use of USP in the title of the product and implementation of Section 126 of FDAMA have been included in our labeling.

2. The comments regarding the container (100's, 500's and 1000's) have been implemented.

3. We have revised our insert labeling using the latest approved insert labeling from Mylan Pharmaceuticals Inc. (approved May 16, 1997) for guidance. We have also included your recommendations regarding the boxed warning, description, how supplied and general comments.

Included with this amendment are twelve (12) copies of final printed container labels and insert labeling which reflect the revisions mentioned above. To facilitate review of our submission and in accordance with 21 CFR 314.94(a)(8)(iv), we are providing a side-by-side comparison of our proposed labeling with the last submitted labeling. Please refer to **Attachment 8.**

Thank you for your time and attention with this matter. Should you have any questions or require any additional information, please do not hesitate to contact either Ms. Debbie Pakay or myself at (973) 515-4059.

Sincerely,

Deborah Pakay /for

Jairaj U. Mehta
Vice President, Regulatory Affairs

JUM/dp

F:\worddata\andas\75284-3

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (201) 386-5566 ● (800) 922-0547

NEW CORRESP

NC

January 26, 1998

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

Re: Ketorolac Tromethamine Tablets USP, 10 mg, ANDA #75-284
Amendment to an Original Application Submission

Dear Sir/Madam:

This letter is in response to the telephone conversation between Lieutenant Denise Huie and myself earlier today. During this conversation, Lieutenant Huie stated that she needed another copy of the FDA 356h, Debarment Certification and Field Copy Letter with original signatures.

Attached please find a copy of Sidmak's FDA 356h, Debarment Certification and Field Copy Letter with original signatures, for the abbreviated new drug application mentioned above.

Should you have any questions, please do not hesitate to contact either Mr. Jai Mehta or myself at (973) 515-4059. Thank you for your time and attention with this matter.

Sincerely,

Deborah L. Pakay

Deborah L. Pakay
Manager, Regulatory Affairs

RECEIVED
JAN 27 1998
GENERIC DRUGS

ANDA 75-284

Sidmak Laboratories, Inc.
Attention: Jairaj U. Mehta
17 West Street, P.O. Box 371
East Hanover, NJ 07936

FEB 3 1998

Dear Sir:

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

Reference is also made to the telephone conversation dated January 26, 1998 and your correspondence dated January 26, 1998.

NAME OF DRUG: Ketorolac Tromethamine Tablets USP, 10 mg

DATE OF APPLICATION: December 23, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 24, 1997

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:

James Wilson
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

505(J)(2)(a)
acceptable for filing?

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (201) 386-5566 ● (800) 922-0547

75/1/26/98

December 23, 1997

Office of Generic Drugs, CDER/FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Abbreviated New Drug Application
Ketorolac Tromethamine Tablets USP 10 mg

Dear Director, Office of Generic Drugs:

Sidmak Laboratories, Inc. submits today an original abbreviated new drug application ("ANDA") seeking approval to market Ketorolac Tromethamine Tablets USP 10 mg that are bioequivalent to the reference listed drug, Toradol® Tablets manufactured by Syntex/Roche Laboratories pursuant to NDA 19645.

This ANDA consists of the following:

Archival Copy	(Blue Folders, 9 Volumes)
Technical Review Copy - CMC	(Red Folders, 2 Volumes)
Technical Review Copy - Bioequivalence	(Orange Folders, 7 Volumes)

Two additional copies of the analytical methods and method validation package are included in the blue accopress binders.

For more detailed information on the organization of this ANDA, please refer to the Table of Contents. As a preface we are including an executive summary which briefly explains the development of this ANDA.

Sidmak Laboratories, Inc. certifies that the field copy (maroon folders, volumes) of this application which has been forwarded to the New Jersey District Office, is a true copy of the technical section (21 CFR 314.94(a)(9)) contained in the archival and review copies of this abbreviated application.

Please direct any written communications regarding this ANDA to my attention at the above address. Should you have any questions regarding this submission please do not hesitate to contact either Ms. Debbie Pakay or myself at (973) 515-4059. Thank you for your prompt handling of this submission.

Respectfully submitted,

Jairaj U. Mehta
Vice President, Regulatory Affairs

/D. Pakay

RECEIVED
DEC 24 1997
GENERIC DRUGS

Sidmak LABORATORIES, INC.

17 WEST STREET ● P.O. BOX 371 ● EAST HANOVER, NJ 07936 ● TELEPHONE: (201) 386-5566 ● (800) 922-0547

December 23, 1997

Office of Generic Drugs, CDER/FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Abbreviated New Drug Application
Ketorolac Tromethamine Tablets USP 10 mg

Dear Sir/Madam:

Enclosed please find Sidmak's Technical Review Copies (Orange Folders, 7 Volumes) which contain the bioavailability/bioequivalence part (Sections I - VII) for this abbreviated new drug application.

The bioavailability/bioequivalence studies included in this submission are entitled:

Relative Bioavailability Study of Ketorolac Tromethamine 10 mg Tablets Under Fasting Conditions [A randomized, single-dose, two-way crossover design involving 32 healthy male subjects under fasting conditions]
PRACS P97-308, 4 Volumes

A Limited Food Effects Study of Ketorolac Tromethamine 10 mg Tablets
[A randomized, single-dose, three-way crossover design involving 18 healthy male subjects under non-fasting conditions (test and reference) and fasting conditions (test product)]
PRACS P97-309, 3 Volumes

In this Technical Review Copy, we are also including a diskette for each study which contains the concentration and parameter data for that study. The information is found in the files labeled "conc.prn" and "pkparam.prn". A hard copy of this data is also attached.

Thank you for your time and attention to this application.

Sincerely,

Jairaj U. Mehta
Vice President, Regulatory Affairs

/D. Pakay