7-6-87

June 30, 1987

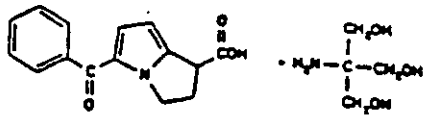
INITIAL PHARMACOLOGY REVIEW

NDA 19-645
Syntex
Palo Alto

Date of Submission: February 6, 1987
Date Received By CDB: February 18, 1987 By Reviewer: February 18, 1987

Drug: Ketorolac Tromethamine (RS-37619-00-21-3)
10 mg tablets

chemical name for ketorolac tromethamine is (+)-5-benzoyl-2, 3-dihydro-1H-pyrrolizine-1-carboxylic acid, 2-amino-2-(hydroxymethyl)-1, 3-propanediol and it has the following structure:



Class of Compound: Pyrrolopyrrole group of NSAIDs.

The composition of the tablet is as follows:

ketorolac tromethamine	10 mg
lactose, NF	
microcrystalline cellulose, NF	
magnesium stearate, NF	

Category: Non-steroidal anti-inflammatory drug
Indication: Analgesic
Related:

Clinical Dosage: 10 mg at 4-6 hour intervals; maximum daily dose is 40 mg.

Patent

U.S. patent No. 4,089,969; expires May 16, 1995. This NDA was originally submitted 10/10/86, received by CDB on 10/16/87. A letter of Refusal to File was sent to them on 12/8/86 because it did not contain 2 carcinogenicity studies. The present submission contains a rat 2-year carcinogenicity study and appears to satisfy animal study requirements.

This submission contains complete animal data on both oral and injection studies, as agreed to in a previous telephone conversation with Dotti Pease. Therefore, this review should be applicable to a new NDA for an injectable ketorolac preparation which the firm intends to submit in the near future. Data from the free acid and the tromethamine salt are submitted because it has been concluded by the firm that their activities, based on the free acid moiety, are equal.

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
ORIGINAL SUMMARY

A. Tests for Analgesic Activity

Phenylquinone-Induced Writhing in Mice

Study AT 1770. Ketorolac, oral 0.05-1.5 mg/Kg. Writhing inhibition activity ID_{50}=0.2 mg/Kg was estimated at 350 times aspirin.

Study AT 1903. Ketorolac tromethamine, oral, 0.075-0.75 mg/Kg; ID_{50}=0.2 mg/Kg. Writhing inhibition estimated at 250 times aspirin.

Study AT 2193. Ketorolac tromethamine, s.c., 0.075-0.75 and 2.25 mg/Kg. Tromethamine salt and free acid were equivalent and were 1.2 fold more potent than orally administered ketoralac.

Phenylquinone-Induced Writhing in Rats

Study AT 1770 ID_{50} (oral) was 0.15 mg/KG, which was 180 times potency of aspirin.

Compression of Yeast-Inflammed Paw

Study AT 1770. Doses tested orally were 0.1-30 mg/Kg. Analgesic action was seen at approximately 1-3 mg/Kg, estimated to be 3 to 10 times more potent than naproxen. Ketorolac did not later alter pain response in non-inflammed paw, indicating that it did not act centrally.

Hot Plate; Mouse

Study AT 1770. Inactive with doses of 1, 7 and 49 mg/Kg. This indicates it did not act centrally or have morphine-like activity.

Binding to Opiate Receptors (In Vitro).

Study AT 3627. Ketorolac did not bind to opiate receptor subtypes κ, δ and μ at doses up to 10^{-3}M.

Adjuvant-Induced Arthritis (Rat)

Study AT 1770 and 2705. ID_{50} (oral) was 0.35 for Ketoralac, which is 400-800 times more potent than aspirin, twice as active as naproxen.

Adjuvant-Inflammed Tail (Rat)

Study 2705. ED_{50} for reduction (orally) was 0.1-0.3; 500 times more potent than aspirin.

Electrical Tail Stimulation (Mouse)

- Study AT 2939. Ketorolac tromethamine, at doses of 12 or 30 mg/Kg was inactive.

Carrageenan-Induced Paw (Edema) Inflation (Rat)

Studies AT 1770, 1990 and 2193. The free acid and ketorolac salt, both had oral anti-inflammatory activity 36 and 118-times phenylbutazone. The free acid was 2.5 times more potent subcutaneously than orally.

Carrageenan-Induced Pleural Effusion (Rat)

Study AT 2705. Ketorolac significantly reduced exudate volume and cell number at 5 and 25 mg/Kg, orally.

Cotton Pellet-Induced Granuloma Formation (Rat)

Study AT 1770 and 2705. No activity seen for Ketorolac (oral) up to 1.5 mg/Kg; it did not prevent granuloma formation.

Yeast Induced Pyrexia (Rat)

Study AT 1770. Ketorolac, orally, was 20-fold more potent than aspirin in anti-pyretic activity.

B. Mechanisms of Action

Thymic Involution (Rat)

Study AT 1770. Ketorolac did not cause thymic involution at doses of 0.02 and 2 mg/Kg, p.o., for 6 days.

Carrageenan Induced Paw Inflammation After Adrenalectomy (Rat)

Study AT 1770. Between 0.03 to 1.0 mg/Kg, p.o., ketorolac caused dose related anti-inflammatory response in adrenalectomized rats.

Prostaglandin Biosynthesis Inhibition (In Vitro)

Study AT 1770. In 3 tests with bull seminal vesicle microsomes, 1 with rabbit renal microsomes and 4 with human platelet microsomes, ketorolac ws consistently 2 to 10 fold more potent than indometharin, including inhibition of PGE_2 and PGF_2 biosynthesis.

Inhibition of Lipogenase Activity (In Vitro)

Study AT 3385. Ketorolac, at concentrations up to 10^{-3}M, did not inhibit lipoxygenase in isolated human polymorphonuclecytes.

Inhibition of Platelet Aggregation, In Vitro.

- Study AT 1770. Ketorolac was a potent inhibitor or arachidonate induced rabbit and human platelet aggregation and of collagen induced human platelet aggregation but had no effect on ADP induced human platelet aggregation.

Inhibition of Platelet Aggregation, In Vivo. Rats and Rabbits

Study AT 1770. Platelet aggregation in capillaries was induced by arachidonate injection, in rats into the left carotid artery to induce cerebral damage and stroke, in rabbits into the ear vein to induce lung damage and respiratory difficulty. Oral doses in rats of 1 and 10 mg/Kg 2 hours prior to arachidonate injection failed to reverse the neurological impairment. In rabbits oral pre-treatment with 0.5 mg/Kg ketorolac or higher reversed the breathing impairment and immobility whereas 0.2 mg/Kg did not.

C. Other Effects; General Pharmacology

Intramuscular Irritation: Rabbit

Studies 2452 and 2738. Based on gross observation, histology and creatinine phosphokinase in serum following injection, 0.25 ml with up to 5% ketorolac tromethamine caused no greater response than vehicle.

Topically Applied on Ear of Mouse

Study AT 2705. Ketorolac at 0.1 and 1.0 mg/mL and ketorolac tromethamine at 0.075 and 0.75 mg/mL, applied daily for four weeks, did not cause irritation to ear where applied.

Ultraviolet-Induced Erythema, Topical, In Guinea Pig

Studies AT 1770 and AT 2705. Ketorolac at 1 and 4 mg dose, in an isopropanol-water gel, caused decreased erythema. Ketorolac tromethamine had less activity than the free acid.

Topically-Induced Burn, Rat

Study AT 1770. At doses of 0.01 and 0.1 mg, topically applied in ethanol to heat-induced burns, ketorolac suppressed the local inflammatory reaction.

Croton Oil-Induced Inflammation, Rat Ear

Studies AT 2705 and AT 2939. Ketorolac, topically applied, inhibited in a dose related manner croton oil-induced inflammation. The tromethamine salt was less active.

Propionibacterium Acnes-Induced Inflammation, Rat Ear

Study AT 3385. Inflammation was induced by injection of heat killed bacteria into ears. Ketorolac tromethamine at 1 mg dose was inactive.

Eye Irritation, Rat

Study AT 2452. Ketorolac tromethamine was more irritating than ophthalmic solution vehicle, based on blinking of eye.

Eye Irritation, Rat, Dog, Monkey

Study AT 2728. Ketorolac did not cause blinking at 0.02 and 0.1% but caused blinking with 0.5% solution in all 3 species. Flurbiprofen caused blinking in all 3 species with 0.1 and 0.5% solutions.

Silver Nitrate-Induced Neovascularization, Rat

Study AT 2728. Ketorolac at 0.25 and 0.5% topically applied, significantly inhibited neovascularization in eye of rat.

Substance P. Induced Uveitis, Rabbit

Study AT 2728. Uveitis was induced by intraocular Substance P injection. Topical application of 0.5 % ketorolac tromethamine in eye was not effective and attributed to too high a dose of Substance P.

Endoxtoxin-Induced Uveitis in Rat (Study AT 3385) and Rabbit (Study AT 2728)

In rat, oral ketorolac tromethamine did not inhibit uveitis but inhibited leucocyte accumulation in aqueous humor. In rabbit, topically applied ketorolac reduced the degree of vascular permeability due to endotoxin of S. typhimurium i.v. injected.

Ocular Inflammation Induced by BW 48/80, Rabbit

Study AT 2728. Topical application of ketorolac prior to challenge with BW 48/80 decreased time to recovery from inflammatory response.

Effect on Intraocular Pressure, Rabbit

Study AT 2728. Ketorolac, topical, prevented decreased ocular pressure due to arachidonic acid.

Lens Aldolase Reductase from Rabbit, In Vitro

Study AT 2728. Inhibition of this enzyme is implicated in cataract development with diabetes and galactosemia. Aspirin salicylic acid, flufenamic acid and naproxen were without effect. Inhibition was caused by indomethacine--67% and ketorolac--30%. The effect by ketorolac was dismissed as "not meaningful."