CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-676

ENVIRONMENTAL ASSESSMENT and/or FONSI

AUG 1 1995

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

ACTRON

KETOPROFEN

TABLETS/CAPLETS

NDA 20-499

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION of Pilot Drug Evaluation

(HFD-007)

FINDING OF NO SIGNIFICANT IMPACT

[NDA 20-499]

[ACTRON]

[KETOPROFEN]

[TABLETS/CAPLETS]

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Ketoprofen Tablets and caplets, Bayer has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

* * *

Ketoprofen is a chemically synthesized non-steroidal anti-inflammatory drug administered orally as a tablet/caplet for the temporary relief of headache, backache, muscular aches, toothache, the minor pain of arthritis, the pain of menstrual cramps, the minor aches and pains associated with the common cold, sore throat, and reduction of fever. It is currently on the US market by prescription only at the strengths of 25 mg, 50 mg, and 75 mg, immediate release capsules and 200 mg extended Release Capsule. Drug substance will be manufactured at S. I. M. S., Italy. Drug product will be manufactured at the Bayer's manufacturing facility at West Haven, CT.

Finished product will be purchased over the counter by the general population throughout the United States and could potentially introduced into the following environments:

a. The environments adjacent to the manufacturing facility at S.I.M.S., Italy,

b. The environments adjacent to the Bayer's manufacturing facility at West Haven, CT.,
c. The environments adjacent to the incineration facility at Clean Harbors Inc. employed for the destruction of waste and returned product:
d. use and disposal by the general public throughout the US.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system. The quantities of substances that will enter the environment as a result of the proposed action are insignificant.

The recommended dose of one or two tablets (or caplets) equivalent to 12.5 mg to 25,0 mg of ketoprofen, is predominately metabolized by glucuronide conjugation, less than 1% is the unchanged drug. Ketoprofen metabolites are not active.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Bayer Corporation has received authorization from the appropriate authorities to operate the plant and has provided certification that operation is in accordance with applicable environmental regulations.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

Attachments: MSDS "Material Safety Data Sheet (Drug Substance)" (provided on page 3-3B-14)

Statements of compliance with emission and environmental requirements are provided on page 3-3B-79 as Appendix C..

Production authorization/Italian government

July 24, 1995
DATE

PREPARED BY
Bart Ho
Review Chemist
HFD-007

7/26/95
DATE

DIVISION CONCURRENCE
Peer Reviewer
HFD-007

8/1/95
DATE

Approved
Environmental Scientist
HFD-004
Center for Drug Evaluation and Research

8/1/95
DATE

Concurred
Robert Jerussi, Ph. D.
Associate Director for Chemistry
HFD-004
Center for Drug Evaluation and Research

CC: Original NDA 20-499/HFD-007
Division File
FONSI File NDA 20-499/HFD-004
Docket File//HFD-004
FOI Copy/HFD-019

File #: FONSI\N20499FO.NSI

APPEARS THIS WAY
ON ORIGINAL

ACTRON® (ketoprofen tablet/caplet) 12.5 mg)

NDA SECTION 3.3B

FOI'ABLE ENVIRONMENTAL ASSESSMENT

Societa Italiana Medicinali Scandicci (S.I.M.S.)
Florence, Italy

Bayer Corporation, Pharmaceutical Division
West Haven, CT

PACO Packaging Inc.
Lakewood, NJ

ACTRON® (ketoprofen tablet/caplet) 12.5 mg)

NDA SECTION 3.3B

FOI'ABLE ENVIRONMENTAL ASSESSMENT

Table of Contents

ENVIRONMENTAL ASSESSMENT INFORMATION

KETOPROFEN 12.5 MG TABLETS/CAPLETS

1. DATE:

June 27, 1995

2. NAME OF APPLICANT:

Bayer Corporation, Consumer Care Division

3. ADDRESS:

1884 Miles Avenue, Elkhart IN 46514

4. DESCRIPTION OF THE PROPOSED ACTION:

a. Description of Proposed Requested Approval:

The proposed action is approval of the New Drug Application 20-499 for Ketoprofen Coated Tablet 12.5 mg and Ketoprofen Coated Caplet 12.5 mg.

b. Need for Action:

Approval of the NDA will make ketoprofen available to the general public as an OTC analgesic. The product will be used by consumers throughout the United States.

c. Location Where the Drug Will be Produced:

i. S.I.M.S., Italy - Ketoprofen drug substance will be produced at the Societa Italiana Medicinali Scandicci (S.I.M.S.) facilities located in Florence, Italy as described in Type II DMF 6997 for Ketoprofen and Type I DMF 6734 for S.I.M.S. S.r.1.

ii. Bayer, West Haven CT - The drug product will be manufactured in existing pharmaceutical production facilities at Bayer Corporation, Pharmaceutical Division, 400 Morgan Lane, West Haven CT 06516. The plant lies in a urban setting with a generally flat to slightly hilly terrain and a temperate climate.

iii. PACO, Lakewood NJ - Packaging and labeling of the drug product will be conducted as PACO Packaging Inc., 1200 Paco Way, Lakewood NJ. The facilities are described in Type I DMF 3347 for PACO Packaging Inc. The plant is located in an urban setting with a generally flat to slightly hilly terrain and a temperate climate.

d. Location Where the Drug Will be Used and Disposed of:

i. S.I.M.S., Italy - Ketoprofen drug substance will be transported from Florence, Italy to the Bayer, West Haven site for use in drug product manufacture. Any unacceptable material will be returned to S.I.M.S.

ii. Bayer, West Haven CT - The facility at which the product is manufactured is subject to the following requirements:

All returned goods and manufacturing waste products will be collected for disposal under the direction of the Office of the Manager of Environmental and Safety Affairs. Disposal is by incineration via a manifested isolated disposal program. Currently, the major incineration facility used for destruction of returned goods is Clean Harbors Inc. at 385 Quincy Avenue, Braintree MA.

Clean Harbors holds a Part A Permit (no expiration date) for hazardous waste treatment, transfer, and recovery with EPA facility identification number MAD053452637. Clean Harbors is on Interim Status as a Part B permit facilty awaiting final EPA Region 1 approval. The facility is situated in an industrial urban setting on the waterfront in the greater Boston area.

iii. PACO, Lakewood NJ - Bulk tablets will be transported from Bayer, West Haven CT for packaging at PACO using the following materials:

Bottles:	white high density polyethylene
Caps:	white and natural polypropylene
Liners:	pulp/white sulfite paper/wax
Seals:	aluminum/polyester/polyethylene
Foil:	polyester/polyethylene/aluminum/low density polyethylene
Labels:	printed pressure-sensitive paper
Cartons:	printed paper board

Tablet spills and scrap packaged product will be collected and returned to Bayer, West Haven CT for disposal as indicated in the previous section. The packaging materials should not produce toxic dioxane upon burning.

iv. Consumers - The drug product will be purchased

over-the counter by the general public throughout the United States. Expired product held by distributors and retailers will be returned to Bayer, West Haven CT for disposal. Consumer wastes will be disposed of through local household trash collection.

5. IDENTIFICATION OF CHEMICAL SUBSTANCE THAT IS THE SUBJECT OF THIS PROPOSED ACTION:

Description: White or almost white, odorless, nonhygroscopic crystalline powder.

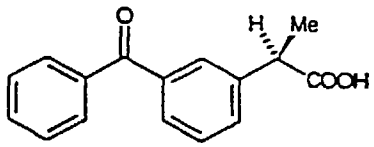
Nonproprietary Name: ketoprofen

Chemical Names: 2-(3-benzoylphenyl) propionic acid, m-benzoylhydratropic acid, 3-benzoyl-α-methylbenzeneacetic acid

CAS Number: 22071-15-4

Molecular Formula: Empirical $C_{16}H_{14}O_3$

Structural



Molecular Weight: 254.29

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

a. Substances Expected to Be Emitted, Controls Exercised, and Compliance with Emissions Requirements:

i. S.I.M.S., Italy - Introduction of substances into the environment is limited by the controls in place at the S.I.M.S. facility, e.g., pollution prevention plant and waste water purification, gas purification and solid residues disposal systems. All emissions are treated in compliance with the local laws and are within the limits stated by the regulations of the Italian Government.

Authorization to produce ketoprofen is indicated in a letter (code number 12737) from the Italian Health Authorities found in appendix a.

ii. Bayer, West Haven CT - The activities associated with the ketoprofen drug product that take place at the West Haven site include sizing, mixing, granulating, drying, compression, aqueous film coating, and bulk packaging.

All manufacturing and packaging operations are performed in compliance with Current Good

Manufacturing Practices.

All liquid and solid waste generated from the manufacturing and packaging of the drug product will be managed in such a fashion as to have no significant impact upon the production facilities compliance permit status relative to all federal, state, and local environmental and safety laws and regulations.

iii. PACO, Lakewood NJ - No emissions are expected from the routine packaging process at the PACO site. Any product accidentally spilled is vacuumed up and placed in a sealed container and returned to Bayer, West Haven CT for disposal. The small amount of dust particles emitted are trapped on the air filters provided by the air handling system.

iv. Consumers - The product will be used by consumers throughout the United States. The recommended dose of one or two tablets (or caplets) equivalent to 12.5 mg to 25.0 mg of ketoprofen, is predominately metabolized by glucuronide conjugation. Virtually all of the material eliminated into the urine after an oral dose is in the form of ketoprofen conjugates, less than 1% is the unchanged drug. Ketoprofen metabolites are not active.

b. Estimate of Quantities of Substances Expected to Enter Environment:

i. S.I.M.S., Italy - No significant quantities of ketoprofen should be emitted.

ii. Bayer, West Haven CT - Because of manufacturing controls, e.g., dust collection systems, pH treatment of waste water, and containment and disposal of solid waste by incineration, no significant quantities of chemical substances are expected to be emitted into the environment.

It is estimated that material losses incurred during the manufacture of the tablets and caplets will be in the range of 1600 kg annually (less than 10% consisting of ketoprofen drug substance), with approximately one-third, or 530 kg, directly accounted for as weighed tablet scrap. The remaining solids, approximately 1065 kg, will be loose powder and granulate. More than 90% of this material will be scooped up or vacuumed away prior to the commencement of equipment and room cleaning. Airborne dust will be collected during manufacturing by various in-line vacuum systems and by processing area air handling systems.

The dust collection systems in the facility use primarily pleated filter media of at least 95% efficiency. Air from operations, e.g. tablet compression, involving the most airborne particulates is HEPA filtered (99.97% efficiency at a 0.5μ level) before being exhausted. Used filters are currently disposed of by incineration at Clean Harbors, Inc.

iii. PACO, Lakewood NJ - No significant quantities are expected to be emitted. Any waste generated from the packaging of the drug product will be managed in such a fashion as to have no significant impact upon the facilities compliance permit status relative to all federal, state, and local environmental and safety laws and regulations.

iv. Consumers - Based on a normal daily dose of 100 mg per patient, a 1% excretion of unchanged ketoprofen, and an average daily water use of 150 liters per household, a concentration of 0.007 ppm per patient can be expected.

c. Effect of the Approval of the Proposed Action on Current Emissions:

The quantities of substances that will enter the environment as a result of the proposed action are insignificant.

The manufacture of ketoprofen drug substance, tablets, and packaged product at the three locations should therefore have no effect on compliance with existing applicable emission requirements (including occupational) at the federal, state, or local level. No modifications of any existing permits will be necessary.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT:

a. Air - No significant concentrations of substances will be emitted at any of the locations, therefore no significant impact is expected.

b. Fresh Water, Estuarine and Marine Ecosystems

i. S.I.M.S., Italy - All waste waters will be treated in S.I.M.S. own waste water purification plant, therefore no significant impact is expected.

ii. Bayer, West Haven CT - No substances to be emitted directly. All wash waters are discharged to the town operated waste water treatment plant under State of CT DEP application SP0000141, expiration date 7/31/95 (application renewal filed 2/28/95).

iii. PACO, Lakewood NJ - No substances to be emitted

directly. All wash waters are to be discharged to the town operated waste water treatment plant.

c. Terrestrial Ecosystems

i. S.I.M.S., Italy - All solid residues are sent to an authorized company for appropriate treatment, therefore no significant impact is expected.

ii. Bayer, West Haven CT - Unused bulk packaging, bulk tablet residuals and rejected tablets and dust collected will be incinerated. The small amounts of inert ingredients remaining in the ash after incineration will pose no threat to a landfill environment.

iii. PACO, Lakewood NJ - All factory waste such as cardboard, paper, plastic, and foil are removed by an approved trash disposal service. Any product waste is returned to Bayer, West Haven CT.

d. Physical Properties Ketoprofen:

Melting Range: 92.0 - 96.0 °C

Water Solubility: 0.21 mg/mL at 37 °C

pH: 6.5 for a 3.95×10^{-4} M solution in water

Dissociation Constant:

	pKa
dioxane: water (2:1)	7.2
methanol: water (3:1)	5.937

Partition Coefficient:

0.105	n-octanol/water (phosphate buffer pH 7.35 and initial ketoprofen concentration of 0.2542 mg/mL)
0.97	(MacIlvaine's buffer pH 7.4 and initial ketoprofen concentration of 0.0240 mg/mL)

Photolysis: There is no direct photolysis, since there is no significant absorption in wavelength above 290 nm.

Absorption Spectrum:

UV max (MeOH) 255 nm

	(H_2O)	261 nm
	($MeOH:H_2O$, 3:1)	281 nm

Hydrolysis: Studies at 50 °C for 5 days show no significant change.

pH 5.0	0.8% hydrolysis
pH 7.0	0.5% hydrolysis
pH 9.0	0.0% hydrolysis

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES:

No significant quantities of ketoprofen are expected to be emitted at S.I.M.S., Bayer, or PACO.,

The landfilling of the non-hazardous components such as paper products will have no adverse effect on the environment. Solid manufacturing wastes and returned goods will be disposed of by incineration. Waste water will be discharged to private or municipal water treatment facilities.

Based on the above, it is concluded that no significant environmental effects are anticipated.

9. USE OF RESOURCES AND ENERGY:

a. S.I.M.S., Italy - In addition to the raw materials that go into the production of ketoprofen, paper, fiber products, and plastics will be used in the bulk packaging process.

This product application will not significantly increase or alter the use of resources or energy at the production site.

There will be no effects upon endangered or threatened species.

b. Bayer, West Haven CT - In addition to the use of raw materials that go into the product, plastics and paper resources will be used in the manufacture and bulk packing of this product. Electricity supplied by the local utility company is used to run all equipment.

The manufacturing of ketoprofen tablets will represent a very small percentage of the total production at the West Haven facility, therefore, this product application will not significantly change the use of resources and energy as compared to the existing normal daily activities.

There will be no effects upon endangered or threatened species or property listed or eligible for listing in the National Register of Historic Places.

c. PACO, Lakewood NJ - Plastic, foil and paper resources will be used in the packaging and labeling of the

product. Electricity are the only energy sources used. This product application will not significantly change the use of resources and energy as compared with existing normal daily activities at the PACO Packaging site.

There will be no effects upon endangered or threatened species or property listed or eligible for listing in the National Register of Historic Places.

10. MITIGATION MEASURES:

Standard material handling measures in each of the three facilities ensure compliance with all environmental regulations.

There are no mitigating measures taken as there are no significant potential adverse environmental impacts associated with the proposed operation.

11. ALTERNATIVES TO THE PROPOSED ACTION:

No significant adverse environmental impacts from this proposed action are expected. Potential enhancement of public health by use of this drug substance far outweigh the negligible potential risks to the environment from the proposed action. Therefore, no alternatives are proposed.

12. LIST OF PREPARERS:

This assessment was prepared by Gary G. Toczylowski, Manager of Environmental and Safety Affairs at Bayer Corporation, Pharmaceutical Division, West Haven CT. He is familiar with the operations to be carried out and knowledgeable of the wastes to be generated. The following individuals also contributed to the compilation of this document:

Tana Carpenter — Senior Q.A. Development Scientist
Bayer Consumer Care Division, Elkhart IN

John Contario — Manager of Analytical Development (former)
Bayer Consumer Care Division, Elkhart IN

13. CERTIFICATION:

The undersigned certifies that the information presented is true, accurate and complete to the best of the knowledge of the departments responsible for preparation of the environmental assessment.

Gary G. Toczylowski — 6/27/95
Gary G. Toczylowski — Date
Manager of Environmental and Safety Affairs
Bayer Corporation, Pharmaceutical Division
West Haven, CT

14. REFERENCES

a. Material Safety Data Sheets (S.I.M.S. and Sigma Chemical Company)

b. The Merck Index, 11th Edition (Rahway, NJ: Merck Co., Inc. 1989) p. 836.

c. Gary G. Liversidge, "Ketoprofen," Analytical Profiles of Drug Substances, 10 (Academic Press, Inc., 1981), p. 443-471.

d. "Ketoprofen," British Pharmacopoeia 1993, vol. I, page 372, and Addendum 1994 page 1345.

e. "Ketoprofen," Pharmacopeial Forum, May-June 1990. (The United States Pharmacopeial Convention, Inc. 1990) p. 439-441.

f. "Ketoprofen," Pharmacopeial Forum, Mar.-Apr. 1994. (The United States Pharmacopeial Convention, Inc., 1994) p. 7195-7199.

15. APPENDIX

a. S.I.M.S. description of pollution prevention plant and Italian Government letter authorizing production of ketoprofen

b. Description of Clean Harbors Inc. Facility

c. Bayer Corporation Environmental & Safety Compliance Statement

d. Bayer, West Haven CT Regulatory Overview (Environmental)

e. Curricula Vitae: Gary Toczylowski, Tana Carpenter, and John Contario

MATERIAL SAFETY DATA

SECTION I

MANUFACTURER'S NAME: SIMS SpA - Società Italiana Radiofarmaci	EMERGENCY TELEPHONE #: 055-8630
FULL ADDRESS: Località Filarone 50066 Reggello - ITALY	
CHEMICAL NAME & SYNONYMS: 2,3-benzoil-phenyl propionic acid	TRADE NAME & SYNONYMS: KETOPROFEN
CHEMICAL FAMILY	FORMULA: $C_{16}H_{14}O_3$
PRODUCT'S USES (SPECIFY): Antinflammatory drug	
SUPPLIER:	
FOR OTHER INFORMATION CALL	INFORMATION EFFECTIVE AS OF

SECTION II HAZARDOUS INGREDIENTS OF MIXTURES

PRINCIPAL HAZARDOUS COMPONENT(S)	%	TLV (UNITS)

SECTION III PHYSICAL DATA

BOILING POINT (° F)	Not app.	SPECIFIC GRAVITY (H2O=1)	--
VAPOUR PRESSURE (mm Hg.)	--	% VOLATILE BY VOLUME (%)	--
VAPOUR DENSITY (AIR=1)	--	EVAPORATION RATE (_____=1)	--
SOLUBILITY IN WATER	not soluble	MELTING POINT (° F)	94°C
APPEARANCE AND ODOUR	White odorless powder		

SECTION IV FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (METHOD USED)	----------	FLAMMABLE LIMITS	LEL: / UEL:
EXTINGUISHING MEDIA	After wearing gas-mask, follow normal firefighting procedures		
SPECIAL FIRE FIGHTING PROCEDURES	----		
UNUSUAL FIRE AND EXPLOSION HAZARDS	----		

SECTION V HEALTH HAZARD DATA

THRESHOLD LIMIT VALUE			not indicated
EXPOSURE ROUTES	INHALATION	NO	EFFECTS OF OVER EXPOSURE
	SKIN CONTACT	NO	
	SKIN ABSORPTION	NO	
	EYE CONTACT	Yes	
	INGESTION	YES	

EMERGENCY AND FIRST AID PROCEDURES

Eye contact: abundantly wash with water; skin contact: wash with soap and water; Ingestion: drink salty water and provoke vomit. ~~XX~~ If quantity is ~~not~~ important, refer to first aid center.

SECTION VI – REACTIVITY DATA

STABILITY			CONDITIONS TO AVOID
	UNSTABLE		
	STABLE		

COMPATABILITY (MATERIALS TO AVOID) it can react violently with strongly oxydizing compounds

HAZARDOUS DECOMPOSITION PRODUCTS

SECTION VII SPILL OR LEAK PROCUEDURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED

Gather spilled material at best and wash with abundant water (use mechanical means)

NEUTRALIZING CHEMICALS ===

WASTE DISPOSAL METHOD

SECTION VIII SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION (SPECIFY TYPE)

VENTILATION	LOCAL EXHAUST		SPECIAL
	MECHANICAL (GENERAL)		OTHER

PROTECTIVE GLOVES EYE PROTECTION

OTHER PROTECTIVE EQUIPMENT

SECTION IX SPECIAL PRECAUTIONS

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORING Use normal precautions in handling chemicals pharmaceutically active. Use antidusk mask, and operate nearby an aspiration device.

OTHER PRECAUTIONS Avoid skin contact.

Store material in well-closed containers, away from sources of light and ~~extreme~~ heat.

NAME Dr. Nidiaci DATE 02/09/1987

Technical Director

N.A. NOT APPLICABLE

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NDA 20-100607

ATTN: SAFETY DIRECTOR
MILES INC
400 MORGAN LANE
WEST HAVEN CT 06516-4175

EMERGENCY PHONE 1-314-771-5765

DATE: 06/04/93
CUST#: 4-013-57120
PO#: HB441EW26
19887

MATERIAL SAFETY DATA SHEET

- - - - IDENTIFICATION - - - -

PRODUCT #: K1751
CAS #: 22071-15-4 NAME: KETOPROFEN
MF: C16H14O3

SYNONYMS
L*ACIDE (BENZOYL-3-PHENYL)-2-PROPIONIQUE (FRENCH) * ALRHEUMAT * ALRHEUMUN * BENZENEACETIC ACID, 3-BENZOYL-ALPHA-METHYL- * M-BENZOYLHYDRATROPIC ACID * 3-BENZOYLHYDRATROPIC ACID * 3-BENZOYL-ALPHA-METHYLBENZENEACETIC ACID * 2-(M-BENZOYLPHENYL)PROPIONIC ACID * 2-(3-BENZOYLPHENYL)PROPIONIC ACID * CAPISTEN * FASTUM * ISO-K * KEFENID * KETOPROFEN * KETOPRON * LERTUS * MEPROFEN * ORUDIS * ORUVAIL * PROFENID * 19583 RP *

- - - - TOXICITY HAZARDS - - - -

RTECS #: UE7570000
PROPIONIC ACID, 2-(3-BENZOYLPHENYL)-

TOXICITY DATA

ORL-RAT LD50:62400 UG/KG	ARZNAD 34,280,84
IPR-RAT LD50:80 MG/KG	NIIRDN 6,265,82
SCU-RAT LD50:100 MG/KG	JNPHAG 2,259,71
IVN-RAT LD50:350 MG/KG	IYKEDH 9,222,78
REC-RAT LD50:94 MG/KG	JTSCDR 6,209,81
ORL-MUS LD50:360 MG/KG	PJPPAA 38,107,86
IPR-MUS LD50:300 MG/KG	EJMCA5 11,7,76
SCU-MUS LD50:550 MG/KG	JNPHAG 2,259,71
IVN-MUS LD50:500 MG/KG	JNPHAG 2,259,71
ORL-GPG LD50:1300 MG/KG	JNPHAG 2,259,71
IVN-GPG LD50:450 MG/KG	JNPHAG 2,259,71

REVIEWS, STANDARDS, AND REGULATIONS
EPA TSCA CHEMICAL INVENTORY, JUNE 1990

TARGET ORGAN DATA
BRAIN AND COVERINGS (OTHER DEGENERATIVE CHANGES)
BEHAVIORAL (HEADACHE)
GASTROINTESTINAL (ULCERATION OR BLEEDING FROM SMALL INTESTINE)
GASTROINTESTINAL (NAUSEA OR VOMITING)
GASTROINTESTINAL (PERITONITIS)
KIDNEY, URETER, BLADDER (CHANGES IN TUBULES)
MATERNAL EFFECTS (OVARIES, FALLOPIAN TUBES)
MATERNAL EFFECTS (UTERUS, CERVIX, VAGINA)
SPECIFIC DEVELOPMENTAL ABNORMALITIES (CARDIOVASCULAR SYSTEM)
ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS) DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR

CONTINUED ON NEXT PAGE

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OUTSIDE USA/CANADA call COLLECT 314-771-5750

CUST#: 4-013-57120
PO#: HB441EW26
19887

PRODUCT #: K1751
CAS #: 22071-15-4 NAME: KETOPROFEN
MF: C16H14O3

- - - - TOXICITY HAZARDS - - - -

COMPLETE INFORMATION.

- - - - HEALTH HAZARD DATA - - - -

ACUTE EFFECTS
HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.
THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPICUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT, CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

- - - - PHYSICAL DATA - - - -

MELTING POINT: 94°C

APPEARANCE AND ODOR
SOLID.

- - - - FIRE AND EXPLOSION HAZARD DATA - - - -

EXTINGUISHING MEDIA
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO PREVENT CONTACT WITH SKIN AND EYES.

- - - - REACTIVITY DATA - - - -

CONTINUED ON NEXT PAGE

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CUST#: 4-013-57120
PO#: HB441EW26
19887

PRODUCT #: K1751
CAS #: 22071-15-4 NAME: KETOPROFEN
MF: C16H14O3

- - - - REACTIVITY DATA - - - -

STABILITY
STABLE.

INCOMPATIBILITIES
STRONG OXIDIZING AGENTS

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
CARBON MONOXIDE, CARBON DIOXIDE

HAZARDOUS POLYMERIZATION
WILL NOT OCCUR.

- - - - SPILL OR LEAK PROCEDURES - - - -

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED
WEAR RESPIRATOR, CHEMICAL SAFETY GOGGLES, RUBBER BOOTS AND HEAVY RUBBER GLOVES.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.
WASTE DISPOSAL METHOD
DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.
OBSERVE ALL FEDERAL, STATE AND LOCAL ENVIRONMENTAL REGULATIONS.

- - - - PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE - - - -

NIOSH/MSHA-APPROVED RESPIRATOR.
MECHANICAL EXHAUST.
COMPATIBLE CHEMICAL-RESISTANT GLOVES.
CHEMICAL SAFETY GOGGLES.
LABEL PRECAUTIONARY STATEMENTS
TOXIC
TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE (SHOW THE LABEL WHERE POSSIBLE).
WEAR SUITABLE PROTECTIVE CLOTHING, GLOVES AND EYE/FACE PROTECTION.

CONTINUED ON NEXT PAGE

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THE WORLD'S FOREMOST MANUFACTURER OF RESEARCH BIOCHEMICALS AND DIAGNOSTIC REAGENTS

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- - - - ADDITIONAL PRECAUTIONS AND COMMENTS - - - -

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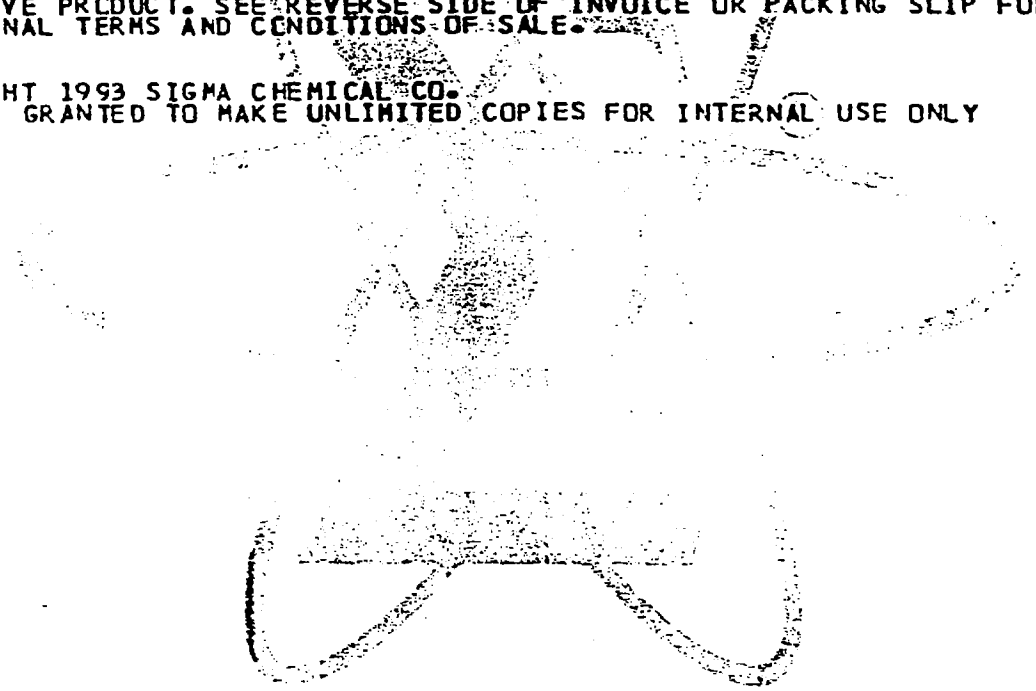


Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

June 26, 1995

Environmental and Safety Compliance Statement

Rwgarding the production of ketoprofen 12.5 mg tablets at its facilities in West Haven, CT, Bayer Corporation states it is compliance with all environmental and safety emissions requirements set forth in applicable permits as well as emissions requirements set forth in applicable federal, state, and local statutes and regulations. There are currently no pending environmental or safety consent decrees and/or administrative orders against this facility concerning any emission standard.

Gary G. Toczylowski
Manager Environmental and Safety Affairs

S.I.M.S.

Società Italiana Medicinali Scandicci

STABILIMENTI CHIMICO - FARMACEUTICI INDUSTRIALI

Sede legale: Via F. G. Angelico, 34 - Firenze

Codice Fiscale e Partita I.V.A. 00076410483

P.O. BOX 390 • 50100 FIRENZE • TELEX 570312 • FAX 055 • 853008

POLLUTION PREVENTION PLANT

WASTE WATER PURIFICATION

The water arrives to the pollution prevention plant through a double sewage system: one used for the water coming from the processes, in acid resistent material, and the other one used for the cooling water and the well water. The water is purified through a chemical and a biological treatment plant.

Purification process:

The waste water is collected into a tank A which can store the waste water produced over a period of 40 hours. In this basin waters coming from several processes are mixed and the solvents separated.

The waste water is then passed into the tank B, where the pH is adjusted to 8.5 with lime or Sulfuric acid. Then flocculants and Ferric chloride are added.

The liquid passes to the decanting tank C, where the precipitated substances are separated, and then to the neutralization tank D. It is then passed to storage tank E, where it is diluted with white waters coming from tank H, which gathers cooling and well waters.

The tank E is used for the first aeration of the liquid and the storage into this tank provides for a continuous flow of waste water, even on holidays, to the bacteria sludge percolator.

The sludge separated in the tank C is sent to the thickener G and then to the filter press.

The water coming from the percolator, after a further dilution with white water in basin H, passes to tank F, containing activated bacteria sludge, where it is purified.

All the biological sludge is sent to the thickener N and then centrifuged.

The residual cakes are discharged to a public facility.

GAS PURIFICATION PLANT

Each of the three synthesis departments, as well as the drying, the pilot and the warehouse dept, are equipped with central aspiration and neutralization plant, connected by pipelines to each single apparatus.

The solid residues are sent to authorized company for the [illegible] treatment.

Ministero della Sanità

DIR.GEN.SER.FARMACEUTICO

N. 600.8/30.61/66-1

Riguarda il Foglio del

N.

Roma 27-9-1991

ALLA DITTA

S.I.M.S.

Località Filarone

50066 REGGELLO (FI)

OGGETTO: Autorizzazione alla produzione di materie prime da usare in medicina.

Visto la documentazioni presentate, codesta Ditta è autorizzata alla produzione dei principi attivi riportati nell'allegato tabulato.

IL DIRIGENTE DELLA DIV.VIII

TRANSLATION

RE: Authorization to the production of raw materials to be used in medicine.

In consideration of the submitted documentations, the a.m. firm is authorized to the production of the active ingredients recorded in the enclosed table.

PAGE 4

S.I.S. DIREZIONE GENERALE DEL SERVIZIO FARMACEUTICO

xx-BANCA-DATI-TECNICA-DEL-FARMACO-xx

INTERROGAZIONE COMPONENTI PRODOTTI DALLA DITTA : 8146

RAGIONE-SOCIALE--S-I-M-S-S.P-A.---SEDE--REGGELLO

CODICE 000050

D.C.I. : 009 MEFENAMIC ACID

D.C.IT. 005-ACIDO-MEFENAMICO

CODICE : 12158

D.C.I. 005-FLUFENAMIC-ACID

D.C.IT. : 001 ACIDO FLUFENAMICO

CODICE 10636

D.C.I

D.C.IT. 001-AMILORIDE CLORIDRATO-BIDRATO

CODICE : 12737

D.C.I. 001-KETOPROFEN

D.C IT. : 002 CHETOPROFENE

PER DATI CHIMICO-FISICI DIGITARE "CH" E UN CODICE COMPONENTE

PER RELAZIONE S.M. DIGITARE "SM" E UN CODICE COMPONENTE

PER PAGINA SUCCESSIVA DIGITARE "SS" SELEZIONE ===>

LF-L005 PREG. AMEE. DATA/ORA 30SET92/10.01.32 MSG=062 J=S-ST=L071C

1.1

JUL 18 1995

MEDICAL OFFICER REVIEW

NDA Number:	20-499
Drug Name:	Ketoprofen OTC
Trade Name:	Actron®
Sponsor:	Bayer Corporation 400 Morgan Lane West Haven, CT 06516-4175 Carl E. Calcagni (VP, Regulatory Affairs) Tel: 203-937-2065 Fax: 203-937-
Date Submitted to FDA:	July 15, 1994
Medical Reviewer:	Christina Fang, M.D.
Secondary Reviewer:	Linda Katz, M.D., M.P.H.
Date Received for Review:	July 28, 1994
Date Completed:	June 26, 1995
Material Reviewed:	One hundred and seventy-three volumes
Drug Class:	NSAID (oral OTC analgesic and antipyretic)
Indication:	Pain and fever
CSO Contact:	David Morgan

7/18/95

Christina Fang, M.D. Date

Peer Reviewer Date 11/8/95

CC: Original NDA # 20-499
HFD-007 / Division File
HFD-007 / Christina Fang
HFD-007 / CSO, D. Morgan
HFD-340
R/D Init. by:
F/T by:

TABLE OF CONTENTS

I. INVENTORY OF CLINICAL STUDIES

INVENTORY OF CLINICAL TRIALS

(See Appendix A1 for abbreviation)

Protocol # Investigator	*Design*	*Drug (mg)*	*Patient (N)*	*Outcome summary*	*Comment*
Dental Pain					
88-1 Cooper	Single-dose double-blind randomized parallel two-center	Keto 25 Keto 12.5 Placebo	48 51 51		The formulation of ketoprofen used in the study was not bioequivalent to the formulation of ketoprofen proposed for marketing.
88-2 Sunshine -Puerto Rico	Single-dose double-blind randomized parallel single-center	Keto 25 Keto 12.5 Placebo	49 51 50		The formulation of ketoprofen used in the study was not bioequivalent to the formulation of ketoprofen proposed for marketing.
S90-002 Sunshine & Marrero -Puerto Rico	Single-dose double-blind randomized parallel single-center	Keto 25 Keto 12.5 Keto 9.375 Keto 6.25 Keto 3.125 Ibu 200 Placebo	35 36 10 36 10 35 36	Design: + Result: ++	In terms of PR, PID, and PRID, significant differences were shown in favor of ketoprofen 12.5 and 25mg over placebo from 0.5 to 6 hours.
S91-008 Mehlisch	Single-dose double-blind randomized parallel single-center	Keto 12.5 APAP 650 Placebo	52 52 51	Design: + Result: ++	In terms of PR, PID, and PRID, significant differences were shown in favor of ketoprofen 12.5mg over placebo from 0.5 to 5 hours.
S92-008 Sunshine & Marrero -Puerto Rico	Single-dose double-blind randomized parallel single-center	Keto 12.5 Ibu 200 Placebo	62 62 62	Design: + Result: ++	In terms of PR, PID, and PRID, significant differences were shown in favor of ketoprofen 12.5mg over placebo from 0.5 to 6 hours.

Protocol # Investigator	*Design*	*Drug (mg)*	*Patient (N)*	*Outcome summary*	*Comment*
S92-009 Mehlisch	Single-dose double-blind randomized parallel single-center	Keto 12.5 ASA 650 Placebo	51 52 52	Design: + Result: +	In terms of PR, PID, and PRID, significant differences were shown in favor of ketoprofen 12.5mg over placebo from 0.75 to 4 hours.
Dysmenorrhea					
S92-001 Fulmer	Double-blind randomized 4-way crossover single-center PRN up to 4 times a day for up to three days	Keto 25 Keto 12.5 Ibu 200 Placebo	71 68 69 70	Design: + Result: ± supportive	In terms of PR, PID, and PRID, significant differences were shown in favor of ketoprofen 12.5 and 25mg over placebo from 2 to 4 hours.
S92-004 Dawood Nelson Gordon	Double-blind randomized 4-way crossover single-center PRN up to 4 times a day for up to three days	Keto 25 Keto 12.5 Ibu 200 Placebo	92 94 92 92	Design: + Result: +	In terms of PR, PID, and PRID, significant differences were shown in favor of ketoprofen 12.5 and 25mg over placebo from 1 to 4 hours.
S92-012 Kisicki DeVries	Double-blind randomized 4-way crossover single-center PRN up to 4 times a day for up to three days	Keto 25 Keto 12.5 Ibu 200 Placebo	93 92 94 93	Design: + Result: ± supportive	In terms of PR, PID, and PRID, significant differences were shown in favor of ketoprofen 12.5 and 25mg over placebo from 2 to 4 hours.

Protocol # Investigator	*Design*	*Drug (mg)*	*Patient (N)*	*Outcome summary*	*Comment*
Fever					
92-002 McMahon	Single-dose double-blind randomized parallel single-center	Keto 25 Keto 12.5 APAP 650 Placebo	30 30 30 30	Design: + Result: +	In terms of average and maximum temperature reduction, significant differences were shown in favor of ketoprofen over placebo. Both ketoprofen 25mg and acetaminophen also performed significantly better than ketoprofen 12.5mg.
S92-003 Schachtel	Single-dose double-blind randomized parallel 14 centers	Keto 25 Keto 12.5 APAP 650 Placebo	28 29 26 29	Design: + Result: +	Significant differences were shown in favor of ketoprofen over placebo in terms of average and maximum temperature reduction.
Actual-Use					
S90-3	Single-blind randomized parallel 150 centers PRN up to 6 tab/24 hr for up to 10 days	Keto 12.5-25 Ibu 200-400	3111 3094	Design: ± Result: ± supportive	Subjects appeared to be satisfied with overall pain relief with either treatments. Ketoprofen 12.5 to 25mg was shown to be safe for OTC usage. The rate of non-compliance to dosing instructions approached 50% and was generally treatment independent and unrelated to the incidence of AEs.

II. OVERALL SUMMARY

A. INTRODUCTION

Ketoprofen is a nonsteroidal anti-inflammatory drug of the arylpropionic chemical class which has both analgesic and antipyretic activities. The mechanism of the pharmacologic properties of ketoprofen, though not fully understood, is suggested to include inhibition of prostaglandin and leukotriene synthesis, antibradykinin activity, and lysosomal membrane stabilization.

Ketoprofen was originally synthesized by Rhone-Poulenc Research Laboratories in Paris in 1967 and was first approved for clinical use in France and the United Kingdom in 1973. Approval in the United States was granted to Wyeth-Ayerst in 1986. Ketoprofen is currently marketed in U.S. under the trade names Orudis (25, 50, and 75mg capsules) and Oruvail (200mg extended-release capsules) for the symptomatic treatment of rheumatoid arthritis and osteoarthritis. Orudis was also approved for the management of pain and primary dysmenorrhea. The recommended starting doses are 25 to 50mg every 6 to 8 hours as necessary for pain and primary dysmenorrhea, and 75mg three time a day (tid) to 50mg four times a day (qid) for rheumatoid arthritis and osteoarthritis. The maximum daily dose should not exceed 300mg for any indications. A smaller initial dose is recommended for smaller individuals, debilitated or elderly patients, or patients with renal or liver impairment. Oruvail is recommended for those individuals requiring 200mg a day of ketoprofen for chronic use.

The Sponsor has produced a 12.5mg tablet formulation of ketoprofen, which is lower than the lowest prescription dose, for over-the-counter (OTC) use. The proposed indications for OTC use are the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, the minor pain of arthritis, the pain of menstrual cramps, and reduction of fever. Twenty-two clinical studies performed in 10183 subjects have been submitted in the NDA to support the efficacy and safety claims of ketoprofen for OTC use. Of these 10183 participants, 5278 received ketoprofen; 3800 received ibuprofen; 703 received placebo; 190 received acetaminophen; 123 received aspirin; and 85 received naproxen. (In the three dysmenorrhea trials, each with 4 treatments given in a crossover fashion, 269 subjects were counted more than once.) Ten of the studies are provided for efficacy review. The remainder are clinical pharmacology studies, dental studies using non-bioequivalent formulations, and foreign studies.

B. EFFICACY RESULTS

1. Dental Pain

The four dental studies reviewed were basically of the same study design: single-dose, double-blind, randomized, placebo-controlled, parallel trials, in which pain relief (PR) and pain intensity (PI) were evaluated every 15 minutes during the first 0.5 or 1 hour, then every 30 minutes (in 2 studies) up to 2 hours, and then at hourly intervals up to 6 hours in patients after extraction of impacted third molars (see Efficacy Review - Dental Pain for details).

All four dental studies had positive outcomes. Ketoprofen 12.5mg was shown to be effective in every study and ketoprofen 25mg in one study (the only study in which ketoprofen 25mg was tested) with respect to PR, pain intensity difference (PID), combined PR and PID (PRID). Statistically significant differences in favor of ketoprofen over placebo were also shown in terms of analgesic onset in 3 of the 4 trials, and in terms of analgesic duration in all 4 trials. The results of these studies provided substantial evidence that ketoprofen is an effective analgesic at proposed 12.5 to 25mg OTC dosage levels.

2. Dysmenorrhea

The three dysmenorrhea trials had exactly the same designs: double-blind, randomized, placebo-controlled, four-way crossover with four treatments: ketoprofen 25mg, ketoprofen 12.5mg, ibuprofen 200mg, and placebo, taking as needed for up to 4 times a day, for up to 3 days. PR and PI were evaluated every 30 minutes during the first hour post-dosing and then hourly up to 4 hours.

In terms of PR, PID, and PRID, ketoprofen 12.5mg and 25mg were shown to be effective in relieving pain associated with primary dysmenorrhea (see Efficacy Review - Dysmenorrhea for details).

3. Analgesic Onset and Duration

Statistically significant differences in favor of ketoprofen over placebo in terms of analgesic onset were shown in 3 of the 4 dental trials, and in terms of analgesic duration in all 4 dental trials. The adequate pain relief starts within 30 minutes; and the analgesic duration ranged from 2 hours to longer than 6 hours (see Efficacy Review - Analgesic Onset,/Analgesic Duration for details).

4. Fever

Two fever studies of ketoprofen using induced fever and natural fever models , respectively, were provided for review. Both were single-dose, double-blind, randomized, placebo-controlled, parallel trials with 4 treatment groups: ketoprofen 25mg, ketoprofen 12.5mg, acetaminophen

650mg, and placebo. In terms of the average and maximum temperature reduction, statistically significant differences were shown in favor of ketoprofen 12.5 and 25mg over placebo in both studies. No substantial evidence in differentiating the 3 active-treatment groups (see Efficacy Review - Antipyretic Studies for details).

5. Dose response

No substantial evidence was provided for a dose-response between various ketoprofen doses tested in terms of their analgesic and antipyretic activities in these studies (see Efficacy Review for details).

6. Efficacy Summary

Substantial evidence was provided to support the analgesic and antipyretic efficacy of ketoprofen 12.5 and 25mg, as demonstrated in dental studies, dysmenorrhea studies, and fever studies.

C. ACTUAL-USE STUDY

The actual-use study was a single-blind, randomized, parallel study, conducted at 143 centers, where subjects were issued 60 tablets of one medication (ketoprofen or ibuprofen) and were instructed to keep a daily record of their use.

The most common indications, for OTC use of ketoprofen 12.5 to 25mg or ibuprofen 200 to 400mg, were headache (>50%), musculoskeletal pain (>20%), and dysmenorrhea (>10%). Subjects received either medication appeared to be satisfied with the overall pain relief.

About 8% of subjects reported a new onset or worse severity of adverse events (AE): most frequently the minor complains of digestive system and nervous system. Most AEs were of mild to moderate severity; no deaths or AEs that were serious or unexpected. Subjects on ketoprofen were shown to have statistically more reports of abdominal pain, headache, dizziness, and insomnia, as well as total counts of drug-related events. The differences in the rates or AE reports of individual symptoms between the two treatments might not be clinically meaningful, since only a very small proportion of subjects reported these symptoms. The study showed that patients with prior history of gastrointestinal disease (in general, excluding peptic ulcer disease) tend to have more reports of minor GI complaints with ketoprofen treatment than with ibuprofen treatment. Females and elderly appeared to have more reports of AEs , but no firm conclusion could be drawn in terms of age-treatment interactions or gender-treatment interactions.

About one third of subjects in each treatment group exceeded the recommended OTC dosing, mostly in the categories of taking more than one tablet at initial dose, having a dosing interval less than 4 hours, or taking more than 6 tablets in 24 hours. The maximum excessive dosing was 350mg in 10 divided doses in 24 hours. The rate of overall non-compliance to the dosing instructions approached 50% and was generally treatment independent. The non-compliance to specific dosing instructions was not shown to be related to the incidence of adverse events in general. Ketoprofen 12.5 to 25mg were considered reasonably safe for OTC usage under the proposed OTC dosing instructions.

D. SAFETY RESULTS

1. Pooled Safety Data from Clinical Trials

The safety data was pooled from 22 clinical trials, 16 of which were single-dose trials. In the six multidose trials, the maximum daily dose of ketoprofen was 150mg for 7 days; and the longest duration was 10 days at 75mg per day. A total of 10183 patients received study medications: 5278 received ketoprofen; 3800 received ibuprofen; 707 received placebo; 190 received acetaminophen; 123 received aspirin; and 85 received naproxen. (In the three dysmenorrhea trials, each with 4 treatments given in a crossover fashion, 269 subjects were counted more than once.)

Over 10% of patients on ketoprofen reported to have one or more adverse events. Most AE occurred in <1% of ketoprofen study population. Fever, chills, headache, dyspepsia, nausea, dizziness and somnolence were reported from 1-2% of subjects received ketoprofen. The relative AE reporting frequencies between the treatment groups seemed to be sample-size dependent. For the treatment groups with more than 3000 subjects (ketoprofen and ibuprofen), the trend of AE report was very similar to that of the actual-use study. Most adverse events reported were mild to moderate in severity and non-serious in nature. There was one report of death in a patient 3 days after he received a single oral dose of ketoprofen 25mg. The event was thought to be primarily due to brain metastasis of melanoma. There was one report of esophagitis and one report of melena. Both were considered ketoprofen-related. There were no reports of peptic ulcer disease, GI perforation, renal insufficiency, or anaphylactic reactions. No specific treatment-gender interactions or treatment-age interactions could be concluded based on these data.

There were 40 cases of drop-outs due to adverse reactions. Of the 25 drop-outs in the ketoprofen group, 50% were due to minor GI symptoms (dyspepsia, nausea, diarrhea, abdominal pain, etc.); and 20% were CNS symptoms (dizziness, somnolence, etc.). Except the fatal case described above, none had serious outcomes. Most events resolved spontaneously (see Appendix C3 - Drop-Outs due to AE for details).

2. Worldwide Safety Surveillance

The most frequently reported adverse events associated with ketoprofen are gastrointestinal and hypersensitivity reactions. Taking both the frequency and seriousness into consideration, the most worrisome drug toxicity is ketoprofen-related major GI complications (GI bleeding or perforation, or both). Based on the review of the 4 recently published foreign epidemiological studies that evaluate major GI complications associated with various NSAIDs, it is suggested that ketoprofen might have somewhat more GI toxicity than a number of other (non-aspirin) NSAIDs at higher prescription dose levels (see Appendix C4 for References). However, no adequate information is available to predict whether this would be the case for ketoprofen used at lower doses, for shorter duration, or in different population groups. Ketoprofen was switched

from OTC back to prescription status in Italy after a single fatal case of anaphylaxis in an asthmatic patient (see Safety Review - World Wide Safety Surveillance under Body as a Whole for details). Although there have not been increased reports of anaphylaxis to the spontaneous reporting systems at FDA and World Health Organization (WHO), anaphylactic reaction is a major safety concern with intermittent use of OTC NSAIDs. Other reactions such as renal, hepatic, hematological, and dermatological toxicity are relatively rare. The safety profile of ketoprofen is similar to ibuprofen, naproxen, and other currently available OTC analgesics in general. There may be some differences in terms of specific drug reactions, but the magnitude of the relative risk between different NSAIDs could not be adequately determined due to the limitations associated with available data.

3. Safety Summary

Ketoprofen 12.5mg and 25mg to be taken as instructed are considered reasonably safe for use OTC.

E. BENEFITS AND RISKS

The therapeutic benefit of ketoprofen to be used OTC was demonstrated in dental, dysmenorrhea, and fever studies for ketoprofen 12.5mg and 25mg. No substantial evidence was provided to show significant differentiations in analgesic or antipyretic efficacy of ketoprofen in comparison with other currently available OTC analgesics/antipyretics used as active-controls in the studies.

The safety profile of ketoprofen is similar to the currently available OTC analgesics. The overall reports of adverse events and the reports of individual adverse events for ketoprofen, used at lower doses and for shorter duration, do not differ dramatically from that of ibuprofen, as shown in actual-use study.

There is a relatively wide safety margin between the recommended maximum daily dose of 75mg for OTC use and the maximum daily dose of 300mg for prescription use. Non-compliance has not been shown to be associated with drug toxicity. Although all OTC drugs can be taken in excessive doses, ketoprofen is not shown to have a greater potential to be used for suicide. The risks of major GI complications are mostly dose- and duration-related. At lower doses of ketoprofen and used for shorter duration, as proposed in OTC dosing instructions, minor upper GI symptoms will probably be more common. The risk of drug-related renal insufficiency is increased in patients with conditions that predispose them to hypovolemia, impaired renal perfusion and impaired renal function. The intermittent use of ketoprofen may lead to possible sensitization with the drug, although there have not been increased reports of anaphylaxis with ketoprofen. In general, ketoprofen seems to be relatively well-tolerated with minimal abuse potential.

In summary, ketoprofen 12.5mg and 25mg are considered to be effective and safe for OTC use.

F. PHASE VI COMMITMENTS

III. EFFICACY REVIEW

THE FORMAT OF THE MEDICAL REVIEW

I. Efficacy Review

A. Analgesic studies
- 1. Under each analgesic indication (or pain model)
  - a. the study design and conduct
  - b. the results of each individual trial
  - c. the conclusion on the drug's effectiveness for the analgesic indication
- 2. Analgesic onset and duration (pooled data from all analgesic trials)

B. Antipyretic studies
- 1. The study design, conduct, and results of each fever model
- 2. The conclusion on the drug's effectiveness for the treatment of fever

C. Overall efficacy conclusion

II. Safety Review

A. Actual-use study
- 1. Study design and conduct
- 2. Result
  - a. overall adverse reactions
  - b. adverse reactions by age and gender
  - c. adverse reactions in patients non-compliant to dosing instructions
- 3. Conclusion

B. Pooled safety data from clinical trials
- 1. Adverse event summary
- 2. Adverse event by age and gender
- 3. Drop-outs due to adverse events

C. World wide safety surveillance
- 1. Under each of the 12 body systems
  - a. adverse reactions listed in present label
  - b. Spontaneous Reporting System (SRS at FDA) data summary
  - c. International Drug Monitoring (WHO) data summary
  - d. discussion on drug toxicity
- 2. Overdose

D. Overall safety conclusion

A. ANALGESIC STUDIES OF KETOPROFEN

1. Ketoprofen for Dental Pain (See Appendix A1 for abbreviation and definition)

Four Protocols (NDA volume 29-36)

Protocol # Investigator	***Design***	***Drug (mg)***	***# of patient - efficacy/safety***	***Evaluation time***
S90-002 Sunshine & Marrero -Puerto Rico	Single-dose double-blind randomized parallel single-center	Keto 25 Keto 12.5 Keto 9.375 Keto 6.25 Keto 3.125 Ibu 200 Placebo	35/35 35/36 0/10 35/36 0/10 35/35 35/36	15, 30, 60, 90 & 120 minutes 3, 3.5, 4, 5, 6 hours
S91-008 Mehlisch	Same as above	Keto 12.5 APAP 650 Placebo	52/52 52/52 51/51	15, 30, 45, 60 minutes and 2, 3, 4, 5, 6 hrs
S92-008 Sunshine & Marrero -Puerto Rico	Same as above	Keto 12.5 Ibu 200 Placebo	62/62 61/62 62/62	15, 30, 45, 60, 90 & 120 mins 3, 4, 5, 6 hrs
S92-009 Mehlisch	Same as above	Keto 12.5 ASA 650 Placebo	51/51 52/52 52/52	15, 30, 45, 60 minutes and 2, 3, 4, 5, 6 hrs

<table>
<tr><td>Study population</td><td colspan="5">Male and female subjects age 16 or older, who underwent surgical removal of one or more impacted third molars</td></tr>
<tr><td>Baseline condition</td><td colspan="5">Post-operative dental pain moderate or severe in intensity (PI≥2)</td></tr>
<tr><td>Rescue medication</td><td colspan="5">Not encouraged within the first hour after dosing. If remedicated within an hour, pain scores were excluded from efficacy analysis. If remedicated after 1 hour, the pain scores for the time interval after remedication were extrapolated.</td></tr>
<tr><td rowspan="5">Raw efficacy data

(on-site evaluation)</td><td colspan="5">PI , PR, global assessment, and time to remedication</td></tr>
<tr><td>Additional data collected</td><td colspan="4">Study number</td></tr>
<tr><td></td><td>S90-002</td><td>S91-008</td><td>S92-008</td><td>S92-009</td></tr>
<tr><td>Onset of meaningful relief by stopwatch</td><td>X</td><td></td><td>X</td><td></td></tr>
<tr><td>Off-set of meaningful relief by stopwatch</td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Pain at least half gone</td><td></td><td>X</td><td></td><td>X</td></tr>
</table>

APPEARS THIS WAY
ON ORIGINAL

Execution

Study #	*Drug (mg)*	*Pt exp (N)*	*Age (yr) Mean (range)*	*Gender (N) M / F*	*Race (N) W/B/O*	*Drop-Outs (N)*			*Excl from PRID analysis (N)*	*Baseline mean PI (N) mod/sev*
						Lack of efficacy	*AE*	*Other*		
90-2	Keto25	35	23(16-39)	9 /26	0/0/35	0	0	0	0	2.89 (4/31)
	Keto12.5	36	22(16-35)	13/23	0/0/36	1	0	0	1	2.89 (4/32)
	Keto9.375	10	25(17-40)	4 /6	0/0/10	0	0	0	10	2.80 (2/8)
	Keto6.25	36	23(16-31)	14/22	0/0/36	0	0	1	1	2.89 (4/32)
	Keto3.125	10	22(18-30)	3 /7	0/0/10	0	0	0	10	2.80 (2/8)
	Ibu200	35	21(16-35)	13/22	0/0/35	0	0	0	0	2.89 (4/31)
	Placebo	36	22(16-32)	9 /27	0/036	0	0	0	1	2.83 (6/30)
91-8	Keto 12.5	52	24(17-53)	24/28	33/4/15	0	0	0	0	2.12 (46/6)
	APAP 650	52	24(16-54)	20/32	34/2/16	0	0	0	0	2.12 (46/6)
	Placebo	51	25(17-44)	25/26	36/5/10	0	0	0	0	2.14 (44/7)
92-8	Keto 12.5	62	22(16-32)	20/42	0/5/57	0	0	0	0	2.81 (12/50)
	Ibu 200	62	23(16-41)	17/45	0/4/58	1	0	0	1	2.81 (12/50)
	Placebo	62	22(16-43)	21/41	0/7/55	0	0	0	0	2.81 (12/50)
92-9	Keto 12.5	51	25(16-48)	19/32	38/1/12	0	0	0	0	2.14 (44/7)
	ASA 650	52	24(17-44)	23/29	43/3/6	0	0	0	0	2.15 (44/8)
	Placebo	52	24(16-41)	20/32	36/2/14	0	0	0	0	2.13 (45/7)

There were no statistically significant differences among treatment groups with regard to demographic characters such as age, gender, height, weight and race, surgical variables such as trauma rating, mean duration of surgery, mean time to test medication from stop of surgery (one exception was study 91-008, where the acetaminophen group took study medication significantly later than the ketoprofen and placebo groups), and number of extractions, as well as the mean baseline pain intensity scores.

Efficacy Results of the Dental Pain Studies

Result - Study S90-002 (See graphs and tables on pages 5.1-5.3)

Statistically significant difference	*Pain parameter*	*Time interval*
Keto25 > PLA Keto12.5 > PLA	PR	0.5 through 6 hours
	PID	0.5 through 6 hours
	PRID	0.5 through 6 hours
Keto6.25 > PLA	PR	1 through 3 hours
	PID	0.5 through 3 hours
	PRID	1 through 3 hours
Keto25 > Keto6.25	PR	0.5 through 6 hours
	PID	0.5 through 5 hours
	PRID	0.5 through 6 hours
Keto12.5 > Keto6.25	PR / PID / PRID	1 through 6 hours
	PID	1 through 6 hours
	PRID	1 through 6 hours

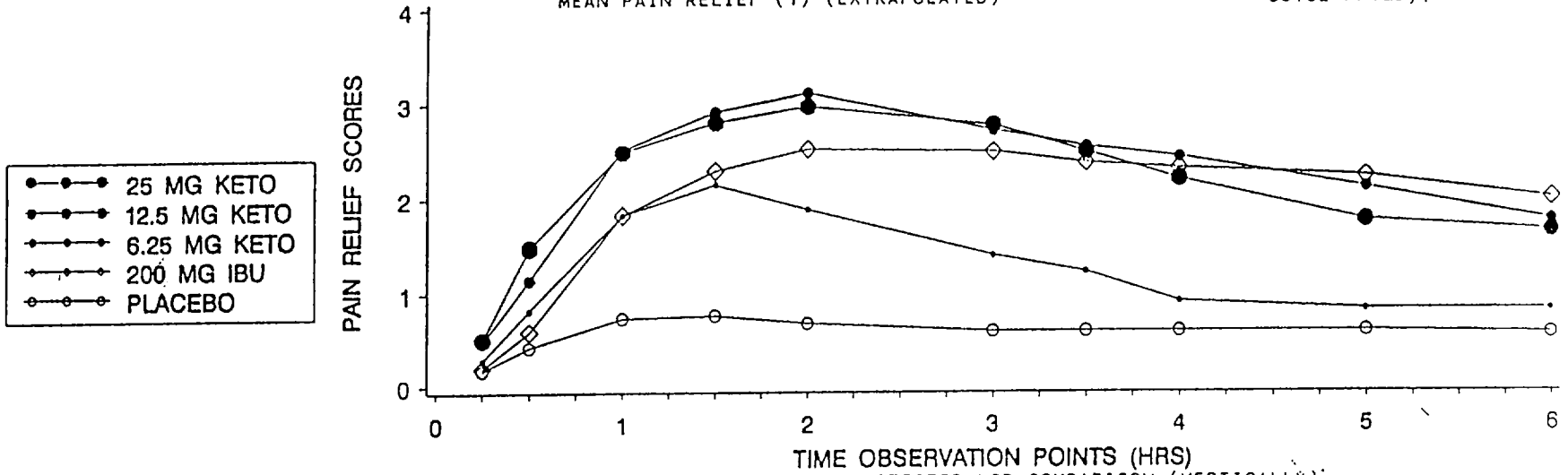
(Note: The statistically significant differences were obtained by applying the Protected Fisher's LSD at the 0.05 level.)

In terms of PR, PID, and PRID, statistically significant differences were shown in favor of ketoprofen 25 and 12.5mg and ibuprofen 200mg over placebo from 0.5 through 6 hours. Ketoprofen 6.25mg statistically performed better than placebo from 1 to 3 hours. There were no meaningful differences between the 3 doses of ketoprofen and ibuprofen 200mg. (Ibuprofen performed statistically better than ketoprofen 6.25mg from 3 to 6 hours: and ketoprofen 12.5 and 25mg performed statistically better than ibuprofen at 0.5 and 1 hour.) Both ketoprofen 25 and 12.5mg performed statistically better than ketoprofen 6.25mg. No statistically significant dose-response was shown between ketoprofen 25 and 12.5mg.

KETOPROFEN (BAY A 7790)/DENTAL
PROTOCOL NO: S90-002

MEAN PAIN RELIEF (1) (EXTRAPOLATED)

09:52 Friday, March 10, 1995

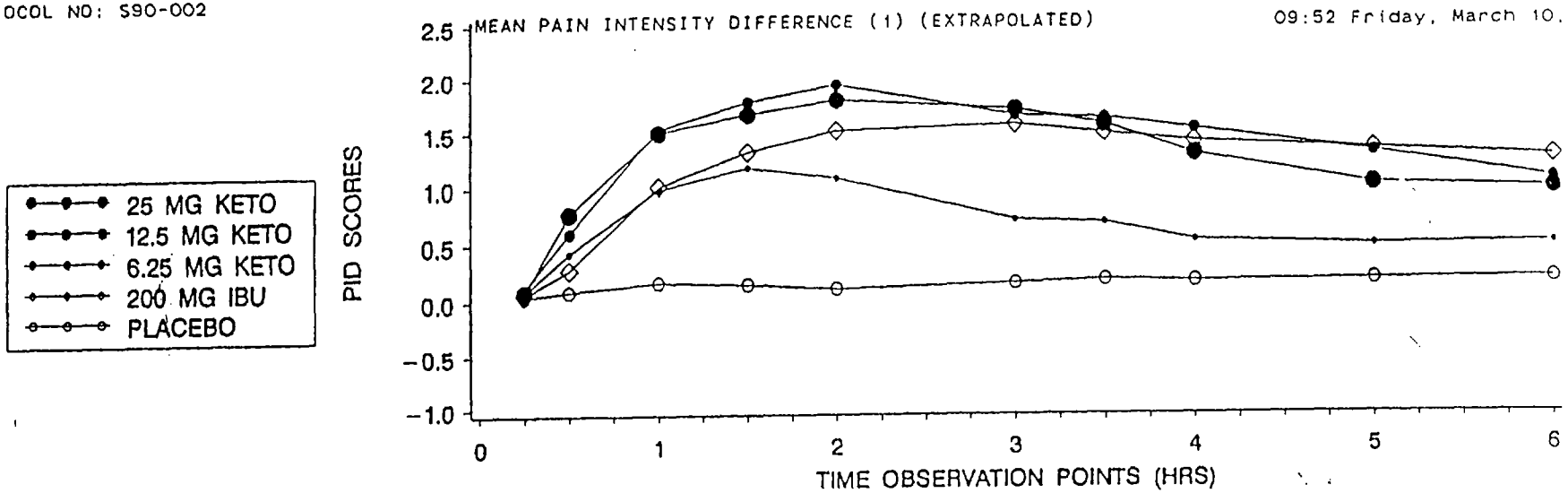


MEANS, (SD), SAMPLE SIZES, AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
FOR PATIENTS VALID FOR EFFICACY ANALYSIS
HOURS

DRUG	.25	.5	1	1.5	2	3	3.5	4	5	6
KETO 25 MG	0.51 (0.85) 35	1.49 (1.25) 35 A	2.49 (1.27) 35 A	2.80 (1.28) 32 AB	2.97 (1.20) 32 A	2.77 (1.46) 31 A	2.49 (1.63) 28 A	2.20 (1.71) 24 A	1.77 (1.75) 19 A	1.66 (1.73) 18 A
KETO 12.5 MG	0.49 (0.82) 35	1.14 (1.03) 35 AB	2.51 (0.98) 35 A	2.91 (1.01) 34 A	3.11 (0.96) 34 A	2.71 (1.30) 31 A	2.54 (1.54) 30 A	2.43 (1.61) 26 A	2.11 (1.68) 24 A	1.77 (1.65) 20 A
KETO 6.25 MG	0.29 (0.57) 35	0.83 (1.01) 35 BC	1.83 (1.27) 35 B	2.14 (1.44) 29 C	1.89 (1.57) 25 B	1.40 (1.58) 19 B	1.23 (1.59) 16 B	0.91 (1.46) 12 B	0.83 (1.36) 11 B	0.83 (1.40) 11 B
IBU 200 MG	0.20 (0.53) 35	0.60 (0.95) 35 C	1.83 (1.42) 35 B	2.29 (1.56) 27 BC	2.51 (1.62) 26 AB	2.49 (1.70) 25 A	2.37 (1.72) 24 A	2.31 (1.68) 24 A	2.23 (1.66) 24 A	2.00 (1.68) 22 A
PLACEBO	0.17 (0.51) 35	0.43 (0.81) 35 C	0.74 (0.95) 35 C	0.77 (1.14) 18 D	0.69 (1.21) 14 C	0.60 (1.31) 7 C	0.60 (1.35) 6 B	0.60 (1.35) 6 B	0.60 (1.35) 6 B	0.57 (1.31) 6 B
TRT P (b)	0.1014	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0003
RMS (b)	0.6739	1.0203	1.1934	1.3015	1.3336	1.4770	1.5721	1.5697	1.5704	1.5636

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
(a) SAMPLE SIZES ARE NOT EXTRAPOLATED
(b) MODEL: PR = u + T(i) + error
(c) PLSD BASED ON MODEL (b) LSMEANS

KETOPROFEN (BAY A 7790)/DENTAL
PROTOCOL NO: S90-002



MEANS, (SD), SAMPLE SIZES, AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
FOR PATIENTS VALID FOR EFFICACY ANALYSIS
HOURS

DRUG	.25	.5	1	1.5	2	3	3.5	4	5	6
KETO 25 MG	0.09 (0.43) 35	0.77 (0.87) 35 A	1.50 (0.92) 35 A	1.67 (0.95) 32 A	1.80 (0.89) 32 A	1.71 (1.10) 31 A	1.57 (1.16) 28 A	1.29 (1.22) 24 A	1.02 (1.18) 19 A	0.98 (1.15) 18 AB
KETO 12.5 MG	0.12 (0.51) 35	0.60 (0.65) 35 AB	1.53 (0.77) 35 A	1.78 (0.76) 34 A	1.94 (0.76) 34 A	1.65 (1.03) 31 A	1.63 (1.13) 30 A	1.52 (1.17) 26 A	1.31 (1.17) 24 A	1.07 (1.11) 20 A
KETO 6.25 MG	0.09 (0.36) 35	0.43 (0.66) 35 B	0.98 (0.91) 35 B	1.18 (1.08) 29 B	1.08 (1.07) 25 B	0.71 (1.10) 19 B	0.68 (1.11) 16 B	0.52 (1.06) 12 B	0.48 (0.98) 11 B	0.50 (0.98) 11 BC
IBU 200 MG	0.06 (0.40) 35	0.28 (0.68) 35 BC	1.01 (1.04) 35 B	1.32 (1.20) 27 AB	1.51 (1.21) 26 AB	1.56 (1.25) 25 A	1.48 (1.29) 24 A	1.41 (1.25) 24 A	1.34 (1.24) 24 A	1.27 (1.21) 22 A
PLACEBO	0.04 (0.37) 35	0.09 (0.53) 35 C	0.17 (0.69) 35 C	0.15 (0.86) 18 C	0.11 (0.95) 14 C	0.15 (0.98) 7 C	0.18 (0.98) 6 B	0.17 (0.98) 6 B	0.18 (0.98) 6 B	0.19 (0.94) 6 C
TRT P (b)	0.9498	0.0005	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0002
T*BASE (c)	0.1460	0.5152	0.8278	0.5666	0.5739	0.8491	0.7532	0.5489	0.4741	0.3703
MS (b)	0.4172	0.6856	0.8740	0.9766	0.9776	1.0945	1.1395	1.1377	1.1165	1.0841

1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
a) SAMPLE SIZES ARE NOT EXTRAPOLATED
b) MODEL: PID = u + T(i) + B(j) + error
c) MODEL: PID = u + T(i) + B(j) + TB(ij) + error
d) PLSD BASED ON MODEL (b) LSMEANS