

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020809

CHEMISTRY REVIEW(S)

**Division of Anti-inflammatory, Analgesic and
Ophthalmic Drug Products
Review of Chemistry, Manufacturing, and Controls**

NDA # 20-809

REVIEW # 1

DATE REVIEWED: 3/20/97

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
SUBMISSION	12-20-96	12-23-96	12-30-96
CORRESPONDENCE	2-10-97	2-18-97	2-28-97

NAME & ADDRESS OF APPLICANT: Alcon Laboratories
6201 South Freeway
Fort Worth, Texas 76134

DRUG PRODUCT NAME

Proprietary: None
Established: Diclofenac sodium
Code Name/#: AL03157A; AL3157A; DCS (Yung Zip)
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: NSAID

DOSAGE FORM: Sterile solution

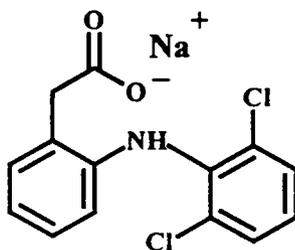
STRENGTHS: 0.1%

ROUTE OF ADMINISTRATION: Ophthalmic

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

2-[(2,6-dichlorophenyl)amino]benzene acetic acid, monosodium salt $C_{14}H_{10}Cl_2NO_2Na$
318.13 CAS 1503-79-6



NDA 20-809 Chemistry #1

REMARKS:

1. The electronic copy of this NDA is incomplete. Various items, ranging from single pages to entire reports are not included but are referenced (to the hard copy).
2. The correspondence contains the CFNs which were omitted in the manufacturing sections.
3. There are several deficiencies in the submission, none of which is "fatal".

CONCLUSIONS & RECOMMENDATIONS:

The CMC section of this NDA is APPROVABLE due to the deficiencies noted in the review.

cc:

Orig. NDA 20-809

HFD-550/Division File

HFD-550/Chemist/Yaciw

HFD-550/CSO/Holmes

HFD-550/Pharm/Coulter

HFD-550/MO/Ludwig


Charlotte A. Yaciw, Chemist, HFD-550/830

 4-28-97
Hasmukh Patel, Chemistry Team Leader HFD-550

filename: N20809C1.REV

**Division of Anti-inflammatory, Analgesic and
Ophthalmic Drug Products
Review of Chemistry, Manufacturing, and Controls**

NDA # 20-809

REVIEW # 2

DATE REVIEWED: 10/15/97

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
[SUBMISSION	12-20-96	12-23-96	12-30-96]
[CORRESPONDENCE	2-10-97	2-18-97	2-28-97]
AMENDMENT (AZ)*	9-10-97	9-11-97	9-22-97

*Item covered by this review

NAME & ADDRESS OF APPLICANT: Alcon Laboratories
6201 South Freeway
Fort Worth, Texas 76134

DRUG PRODUCT NAME

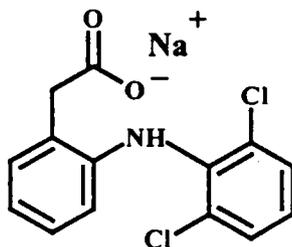
<u>Proprietary:</u>	None
<u>Established:</u>	Diclofenac sodium
<u>Code Name/#:</u>	AL03157A; AL3157A; DCS (Yung Zip)
<u>Chem.Type/Ther.Class:</u>	3S

PHARMACOL. CATEGORY: NSAID

<u>DOSAGE FORM:</u>	Sterile solution
<u>STRENGTHS:</u>	0.1%
<u>ROUTE OF ADMINISTRATION:</u>	Ophthalmic
<u>DISPENSED:</u>	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

2-[(2,6-dichlorophenyl)amino]benzene acetic acid, monosodium salt $C_{14}H_{10}Cl_2NO_2Na$
318.13 CAS 1503-79-6



REMARKS:

1. A NON-APPROVABLE letter was issued 7/29/97 for failure to demonstrate clinical efficacy and safety. CMC deficiencies were included as items 1 through 14 under additional comments and requests. Items 15 and 16 did not originate from the CMC review. The NA letter did not include any comments on labeling.
2. The responses indicate that some of the information requested was available but not filed in the correct sections of the NDA, e.g., the referenced page for the batch formulation reference is in the microbiology section, those for the polyquaternium-1 and _____ are in the executed batch records.

CONCLUSIONS & RECOMMENDATIONS:

From the CMC standpoint, this NDA may be approved contingent on acceptable labeling. The letter should include a statement that the expiration dating period will be 12 months for all sizes.

cc:

Orig. NDA 20-809
HFD-550/Division File
HFD-550/Chemist/Yaciw
HFD-550/CSO/LoBianco
HFD-550/Pharm/Coulter
HFD-550/MO/Ludwig


Charlotte A. Yaciw, Chemist, HFD-550/830

filename: N20809C2.REV


Hasmukh Patel, Chemistry Team Leader HFD-550

**Division of Anti-inflammatory, Analgesic and
Ophthalmic Drug Products
Review of Chemistry, Manufacturing, and Controls**

NDA # 20-809

REVIEW # 3

DATE REVIEWED: 3/12/98

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
[SUBMISSION	12-20-96	12-23-96	12-30-96]
[CORRESPONDENCE	2-10-97	2-18-97	2-28-97
AMENDMENT (AZ)	9-10-97	9-11-97	9-22-97]
AMENDMENT (AZ)*	1-30-98	2-3-98	2-11-98
AMENDMENT (BC)*	2-27-98	3-9-98	FAX
CORRESPONDENCE*	3-3-98	3-4-98	3-6-98
AMENDMENT (BC)*	3-4-98	FAX	FAX

*Item covered by this review

NAME & ADDRESS OF APPLICANT: Alcon Laboratories
6201 South Freeway
Fort Worth, Texas 76134

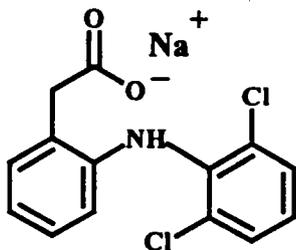
DRUG PRODUCT NAME

Proprietary: None
Established: Diclofenac sodium
Code Name/#: AL03157A; AL3157A; DCS (Yung Zip)
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: NSAID
DOSAGE FORM: Sterile solution
STRENGTHS: 0.1%
ROUTE OF ADMINISTRATION: Ophthalmic
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

2-[(2,6-dichlorophenyl)amino]benzene acetic acid, monosodium salt $C_{14}H_{10}Cl_2NO_2Na$
 318.13 CAS 1503-79-6



REMARKS:

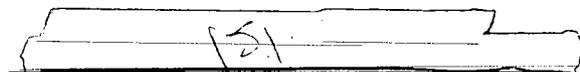
1. An APPROVABLE letter was issued 1/5/98 citing unacceptable labeling, inadequate stability and an incorrect patent reference.
2. The response includes revised labeling (package insert, bottles and cartons) and an updated stability report. The subsequent correspondence and amendments are in response to telephone requests.
3. Methods validation in two FDA laboratories has been initiated.

CONCLUSIONS & RECOMMENDATIONS:

From the CMC standpoint, this NDA may be approved.

cc:

Orig. NDA 20-809
HFD-550/Division File
HFD-550/Chemist/Yaciw
HFD-550/CSO/Gorski
HFD-550/Pharm/Coulter
HFD-550/MO/Chambers


Charlotte A. Yaciw, Chemist, HFD-550/830

filename: N20809C3.REV

 3-1398
Hasmukh Patel, Chemistry Team Leader HFD-550

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020809

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

MAY 12 1997

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR
DICLOFENAC SODIUM
OPHTHALMIC SOLUTION

NDA 20-809

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-550

FONSI for NDA 20-809

CC: Original NDA 20-809/HFD-550
HFD-550/Division File
HFD-550/Chemist/CYaciw
HFD-550/CSO/JHolmes
FONSI File NDA 20-809/HFD-357
Docket File NDA 20-809/HFD-357
FOI Copy/HFD-205

File: n20809fo.nsi

**APPEARS THIS WAY
ON ORIGINAL**

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-809

DICLOFENAC SODIUM

OPHTHALMIC SOLUTION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required to under NEPA to consider the environmental impact of approving certain drug 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 Diclofenac Sodium Ophthalmic Solution Alcon Laboratories has conducted a number of environmental studies and prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a(b)(3) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

* * *

Diclofenac Sodium Ophthalmic Solution is a an aqueous solution of diclofenac sodium administered as an ophthalmic formulation for the management of ocular inflammation. This application allows sale of this product only by prescription. Typically, treatment is for a limited period. Production of the solution will be at the Alcon manufacturing facilities in Fort Worth, Texas. Distribution will be from centers in the U.S.A. prior to sales to pharmacies.

Finished product will be sold in pharmacies, ultimate patient use and disposal will be mainly in residences.

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.

In the United States, unused or expired product will be disposed of by permitted procedures which are described in the environmental assessment. Federal and state waste permits and state air pollution control permits have been issued, when appropriate.

FONSI for NDA 20-809

Empty or partially empty containers will be disposed of as trash by consumers and disposed of by the community's solid waste management system.

Neither the drug substances nor drug product are expected to be introduced into the environment via transportation or storage.

During the drug product manufacturing process at Fort Worth, Texas, waste may result in air emissions, liquid waste streams and solids. Air emissions are controlled by filtering the exhausts. Liquid waste streams are low level and are discharged into a local sewer system. Solid waste will be disposed of off-site at a licensed disposal facility.

Diclofenac sodium and the other components of Diclofenac Sodium Ophthalmic Solution are known not to be volatile and, therefore, release into the air would not be expected from therapeutic use or disposal.

Manufacture of Diclofenac Sodium Ophthalmic Solution represents a portion of the total production at the facilities in Fort Worth, Texas. Land use will not be altered since existing Alcon facilities will be utilized.

* * *

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.

**APPEARS THIS WAY
ON ORIGINAL**

Attachment 4ENVIRONMENTAL ASSESSMENT

- Section for FOI Disclosure -

Drug Product - Diclofenac Sodium Ophthalmic Solution 0.1%

Item 1. Date: December 13, 1996

Item 2. Applicant: Alcon Laboratories, Inc.

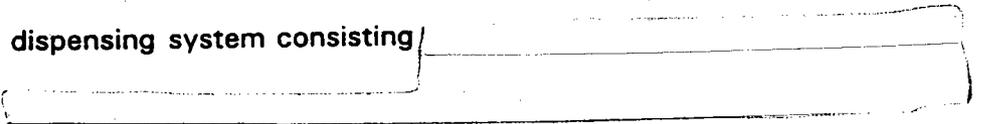
Item 3. Address: 6201 South Freeway
(P. O. Box 6600)
Fort Worth, Texas 76134-2099

Item 4. Description of the Proposed Action:

a. Requested Approval

Pursuant to the provisions of 21 CFR 314.54, a 505 (b)(2) New Drug Application is being submitted for Diclofenac Sodium Ophthalmic Solution, 0.1% (Diclofenac Ophthalmic Solution). The proposed drug product is a sterile, multi-dose, topical ophthalmic solution containing 0.1% diclofenac sodium which is a non steroidal anti-inflammatory agent.

The proposed product will be packaged in a DROP-TAINER® dispensing system consisting



This environmental assessment is being submitted pursuant to 21 CFR 25.31.

b. Need for Action

The proposed product is administered topically to the eyes and is indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

c. Production Locations

1. Drug Substance

We ask that the name and address of the drug substance manufacturer be considered confidential under FOIA procedures.

2. Drug Product

The drug product, Diclofenac Sodium Ophthalmic Solution, 0.1% will be manufactured by the applicant in the approved facility identified above in Item 3.

The manufacturing facility is located in Fort Worth, Texas. The business unit location is approximately 60 acres in an area primarily occupied by light industry, warehousing and distribution operations. The Alcon property is the Corporate Headquarters and a portion of the property is where the manufacturing operation is located. The property is bordered north by a large section, over 50 acres, of undeveloped property. The western section of the property is bordered by a multi lane expressway (I35-W) which runs north and south. The southern perimeter is adjacent to a four lane city road which is used for entrance to the adjacent light

industrial/warehousing park area earlier described. The eastern border is adjacent to a sizable section of acreage, over 50 acres, used for agricultural purposes, grasses and hay for livestock. There have been no major environmental events that have impacted the described site property since the occupancy by Alcon Laboratories, Inc. The original building was constructed in or about 1952 on the property with continued expansion as business requirements have dictated.

d. Locations of Use

The drug product will be available by prescription only and will be used by physicians and patients in a hospital, clinic, or home.

e. Disposal Sites

1. Drug Substance

The drug substance is returned to the vendor for disposal if found to be out of specification as established in the purchasing agreement. Out-of-date drug substance is disposed of by Alcon Laboratories as nonhazardous waste by the permitted solid waste disposer. The facility currently being used is identified in Item 6.

2. Drug Product

- a. Rejected or returned drug product is disposed of by Manufacturing and by the Returned Goods Department housed within Alcon Central

Distribution, respectively. In the case of Diclofenac Ophthalmic Solution, the disposal process is completed by processing the finished product through the controlled use grinding system. The grinding process or bulk product solution is legally captured and discharged to the sanitary sewer system under the discharge permit issued by the City of Fort Worth, acting under both State and Federally granted authority. The plastic containers (ground) are then discharged to the compliantly permitted landfill. Current permits for liquid and solid disposal are detailed in Item 6 of this Environmental Assessment.

- b. Empty or partially empty containers will be disposed of by the user as nonhazardous waste. Typically, they are disposed of through a hospitals, clinics, or communities solid waste management system which could include landfills, incineration, or recycling.

Item 5. Identification of Chemical Substances That are the Subject of the Proposed Action:

a. Nomenclature

1. USAN Name: Diclofenac Sodium

2. Chemical Names:

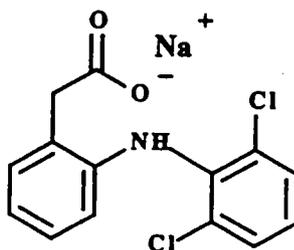
- (a) Sodium [o-(2,6-dichloroanilino)phenyl] acetate
 (b) 2-[(2,6-Dichlorophenyl)amino]-benzeneacetic acid, monosodium salt.

b. CAS Registration Number: 15307-79-6

c. Molecular Formula: $C_{14}H_{10}Cl_2NO_2Na$

d. Molecular Weight: 318.13

e. Structural Formula:



f. Physical Description: White, crystalline powder. Solubility in various solvents at room temperature is as follows:

Solvent	mg/ml
Methanol	> 24
Acetone	6
Acetonitrile	< 1
Cyclohexane	< 1
Water pH 5.2	> 9
Water pH 1.1 (HCl)	< 1
Water pH 7.2 (PO ₄ ⁻ buffer)	6

The partition coefficient of Diclofenac Ophthalmic Solution between n-octanol and aqueous buffer at pH 7 is 13.4.

g. Additives: None

h. Impurities:

This material is protected from disclosure.

Material Safety Data Sheets for the drug substance and drug product are included as Exhibits 1 and 2, respectively.

Item 6. Introduction of Substances Into the Environment

a. Drug Substance

Diclofenac is manufactured outside the United States. In lieu of detailed documentation, a Certificate of Compliance from the manufacturer certifies: 1) compliance with all applicable local and environmental laws; 2) compliance with all emission requirements set forth in all permits applicable to the production of diclofenac, and; 3) that approval and the subsequent increase in production of diclofenac at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

b. Drug Product

Potential environmental hazards addressed for manufacture of the drug product are those emitted into the air, water and land disposal. Waste streams (air, liquid, solid) which emanate as a result of the production of Diclofenac Ophthalmic Solution are reviewed for the purpose of determining if any of the characteristics of said waste are deemed special, hazardous or non-hazardous under the definitions as stated by applicable regulations promulgated and enforced by the United States Environmental Protection Agency, Texas Natural

Resource Conservation Commission and the City of Fort Worth. This method of exercising proper controls is done as a natural step within the compliant production methodology process used within the Alcon manufacturing facility discussed. There is no treatment of any waste product produced within the manufacturing sector. All waste that emanates from the production facility is handled in accordance with applicable environmental regulations and appropriate permits if required. These controls exercised are continually expressed in the various employee safety programs including those under the jurisdiction of the Occupational Safety and Health Administration as written in CFR29-1910.

Air: The processes, including sterilization, used to manufacture Diclofenac Ophthalmic Solution are not of the type that would impact any permitted air emissions from the Alcon manufacturing site.

Environmental air related permits for this product are not necessary. Raw material particulate(s) are captured by internal means via filtration methodology and there are no emissions to the atmosphere discharged as a consequence of the manufacture of Diclofenac Ophthalmic Solution. These controls exercised allow this product to be produced outside required controls directed at permitted air sources, as there are no air emissions. The regulatory precedent is established and recognized by all applicable Federal, State, or Local

environmental regulatory bodies. The permit for relative to all air emissions from the Fort Worth Manufacturing Facility is as follows:

Texas Air Control Board⁵
6330 Highway 290 East
Austin, Texas 78723
Operating Permit No. R-18068
Permit in effect until withdrawn

Water: The by-products and any other wastes pursuant to the making of Diclofenac Ophthalmic Solution are minimal in volume. Any discharge of effluents that would terminate in any public or private water system or reservoir is fully within compliance of all applicable standards.

The City of Fort Worth monitors the liquid discharges of Alcon Laboratories on unannounced basis. The parameters monitored are based on the categorical limits as established by the City of Fort Worth under the categorical guidelines as issued by the Federal and State regulatory agencies. The permit renewal process by the City of Fort Worth includes a yearly process/waste review that determines limits or exclusions of discharges to the sanitary sewer system. Both monitoring and annual permit review establishes the categorical limits by which Alcon operates. Alcon has no "open" regulatory issues and is considered compliant in this regard. The permits relative to waste water are as follows:

⁵Texas Natural Resource Conservation Commission 12100 Park 35th Circle
Austin, Texas 78753

Fort Worth Water Department
 920 Fournier Street
 Fort Worth, Texas
 Permit No. 110
 Renewal: 05/13/97

Texas Water Commission⁶
 1700 North Congress
 Austin, Texas 78701
 Registration No. 65126
 Registration status: Active; valid until amended

Land: The drug product manufacturing facility maintains current registrations for the purposes of general, specific, and hazardous wastes. All wastes are disposed of within the dictates of current regulations by permitted disposers at authorized sites. No treatment of waste is necessary or required on site.

The current solid waste disposer is:

Waste Management, Inc.
 Central Region
 1320 Greenway Drive, Suite 900
 Irving, Texas 75038
 Texas Water Commission Permit No. TWC No. YJ-1019
 Permit in effect until withdrawn

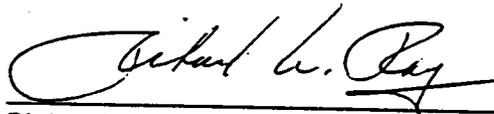
c. Compliance

Citations of applicable Federal, State, and local emission requirements have been provided in Item 6.b.

Alcon Laboratories, Inc. will comply with all current, applicable municipal, state and federal emission standards as they apply in the production of Diclofenac Ophthalmic Solution. The production of

⁶Texas Natural Resource Conservation Commission 12100 Park 35th Circle
 Austin, Texas 78753

same will not affect any current environmentally related permits or employee safety programs as written by The Occupational Safety and Health Administration, United States Department of Labor, within the Alcon Laboratories, Inc. manufacturing facility located in Fort Worth, Texas.



12/16/96

Richard W. Ray
Senior Director
Corporate Safety and Environmental Affairs
Alcon Laboratories, Inc.

Date

d. Effect of Approval on Compliance with Current Emission Requirements

As stated in our compliance statement, the production of Diclofenac Ophthalmic Solution will not adversely affect any current environmentally related permits or employee safety programs.

Items 7-11 This information is not ordinarily required since the proposed action is for NDA approval of a human drug which is for topical ophthalmic application only.

Item 12. List of Preparers

Richard W. Ray

Thomas O. Jones

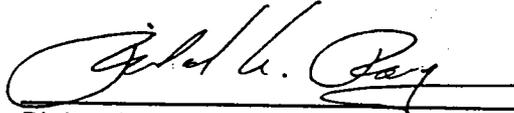
Assisted by Dusty P. Pruitt

Curriculum Vitae for the above are attached.

ALCON WORD PROCESSING CENTER DOCUMENT

Item 13. Certification

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of Alcon Laboratories, Inc.



4/10/97

Richard W. Ray
Senior Director
Corporate Safety and Environmental Affairs
Alcon Laboratories, Inc.

Date

Item 14. References

None

Item 15. Appendices

Exhibits A and B contain disclosable Material Safety Data Sheets.

Exhibit A

MSDS - Drug Substance

MATERIAL SAFETY DATA INFORMATION

2-AUG-1991

***** SECTION I *****

MANUFACTURER/SOURCE OF INFORMATION: SIGMA CHEMICAL COMPANY*

EMERGENCY TEL: 314-771-5765

ADDRESS: P O BOX 14508, ST. LOUIS, MISSOURI 63178

CHEMICAL NAME AND SYNONYMS:

DICLOFENAC SODIUM; BENZENEACETIC ACID, 2-(2,6-DICHLOROPHENYL)AMINO) -,
MONOSODIUM SALT; (O-(2,6-DICHLOROANILINO)PHENYL)ACETIC ACID MONOSODIUM
SALT; (O-(2,6-DICHLOROANILINO)PHENYL)ACETIC ACID SODIUM SALT; VOLTAROL;
CAS NO.: 15307-79-6

NIOSH/RTECS NO.: AG6330000

MOLECULAR FORMULA: C14H10CL2N1NA1O2

CERCLA HAZARD RATINGS (SCALE 0-3):

HEALTH-N/A

FIRE-N/A

REACTIVITY-N/A

PERSISTENCE-N/A

*MSDS DATED 07/05/91

***** SECTION II (COMPONENTS AND CONTAMINANTS) *****

PERCENTAGE: 100%

COMPONENT: DICLOFENAC SODIUM

EXPOSURE LIMITS: NOT LISTED

***** SECTION III (PHYSICAL DATA) *****

HAZARD DESCRIPTION: SOLID

BOILING POINT: NOT LISTED

MELTING POINT: 283-285 C

SPECIFIC GRAVITY: NOT LISTED

VAPOR PRESSURE: NOT LISTED

EVAPORATION RATE: NOT LISTED

SOLUBILITY IN WATER: NOT LISTED

VAPOR DENSITY: NOT LISTED

***** SECTION IV (FIRE AND EXPLOSION HAZARD DATA) *****

FIRE AND EXPLOSION HAZARD: NONE LISTED

FLASH POINT: NOT LISTED

UPPER EXPLOSION LIMIT: NOT LISTED

LOWER EXPLOSION LIMIT: NOT LISTED

FIREFIGHTING MEDIA: WATER SPRAY, CARBON DIOXIDE, DRY CHEMICAL POWDER, ALCOHOL
OR POLYMER FOAM.

FIREFIGHTING: WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING.

GASES PRODUCED: CARBON MONOXIDE, CARBON DIOXIDE, NITROGEN OXIDES,

HYDROGEN CHLORIDE GAS

***** SECTION V (HEALTH EFFECTS AND FIRST AID) *****

*TOXICITY:

ORL-RAT LD50:53 MG/KG	TOIZAG 28,99,81
IPR-RAT LD50:25 MG/KG	NIIRDN 6,311,82
SCU-RAT LD50:83 MG/KG	IYKEDH 5,106,74
IVN-RAT LD50:117 MG/KG	IYKEDH 5,106,74
REC-RAT LD50:85400 UG/KG	YACHDS 114,2259,86
ORL-MUS LD50:125 MG/KG	ARZNAD 34,280,84
IPR-MUS LD50:130 MG/KG	IYKEDH 5,106,74
SCU-MUS LD50:390 MG/KG	NIIRDN 6,311,82
IVN-MUS LD50:116 MG/KG	IYKEDH 5,106,74
UNR-MUS LD50:380 MG/KG	PCJOAU 21,275,87
ORL-DOG LD50:59 MG/KG	KSRNAM 6,1521,72
IVN-DOG LD50:42 MG/KG	KSRNAM 6,1521,72
ORL-RBT LD50:157 MG/KG	KSRNAM 6,1521,72

TARGET ORGAN DATA

BEHAVIORAL (ALTERED SLEEP TIME)
BEHAVIORAL (ANOREXIA, HUMAN)
BEHAVIORAL (ATAXIA)
LUNGS, THORAX OR RESPIRATION (RESPIRATORY STIMULATION)
KIDNEY, URETER, BLADDER (PROTEINURIA)
SKIN AND APPENDAGES (AFTER SYSTEMIC EXPOSURE: DERMATITIS, OTHER)
INTERNAL EFFECTS (TESTES, EPIDIDYMIS, SPERM DUCT)
EFFECTS ON FERTILITY (OTHER MEASURES OF FERTILITY)
EFFECTS ON EMBRYO OR FETUS (FETOTOXICITY)
SPECIFIC DEVELOPMENTAL ABNORMALITIES (CARDIOVASCULAR SYSTEM)
EFFECTS ON NEWBORN (GROWTH STATISTICS)
ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)
DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

INHALATION--

- .HIGHLY TOXIC. ACUTE EXPOSURE: HARMFUL IF INHALED. EXPOSURE CAN CAUSE:
GASTROINTESTINAL DISTURBANCES, NAUSEA, DIZZINESS AND HEADACHE
- .CHRONIC EXPOSURE: POSSIBLE TERATOGEN. OVEREXPOSURE MAY CAUSE REPRODUCTIVE
DISORDER(S) BASED ON TESTS WITH LABORATORY ANIMALS.
- .FIRST AID: IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT,
CALL A PHYSICIAN.

SKIN CONTACT--

- .IRRITANT/TOXIC. ACUTE EXPOSURE: HARMFUL IF ABSORBED THROUGH SKIN. EXPOSURE
CAN CAUSE: GASTROINTESTINAL DISTURBANCES,
NAUSEA, DIZZINESS AND HEADACHE
- .CHRONIC EXPOSURE: POSSIBLE TERATOGEN. OVEREXPOSURE MAY CAUSE REPRODUCTIVE
DISORDER(S) BASED ON TESTS WITH LABORATORY ANIMALS.
- .FIRST AID: IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR

AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND SHOES. CALL A PHYSICIAN.

EYE CONTACT--

.IRRITANT. ACUTE EXPOSURE: NOT LISTED

.CHRONIC EXPOSURE: NOT LISTED

.FIRST AID: 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.

INGESTION--

.HIGHLY TOXIC. ACUTE EXPOSURE: HARMFUL IF INGESTED. EXPOSURE CAN CAUSE: GASTROINTESTINAL DISTURBANCES, NAUSEA, DIZZINESS AND HEADACHE.

.CHRONIC EXPOSURE: POSSIBLE TERATOGEN. OVEREXPOSURE MAY CAUSE REPRODUCTIVE DISORDER(S) BASED ON TESTS WITH LABORATORY ANIMALS.

.FIRST AID: IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS. CALL A PHYSICIAN.

***** SECTION VI (REACTIVITY DATA) *****

STABILITY: STABLE

INCOMPATIBILITIES: NONE LISTED

DECOMPOSITION: PRODUCTS TOXIC FUMES OF CARBON MONOXIDE, CARBON DIOXIDE, NITROGEN OXIDES, HYDROGEN CHLORIDE GAS

POLYMERIZATION: WILL NOT OCCUR

CONDITION TO AVOID: NOT LISTED

***** SECTION VII (SPILL OR LEAK PROCEDURES) *****

PILL: WEAR SELF-CONTAINED BREATHING APPARATUS, 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.

DISPOSAL: 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.

***** SECTION VIII (SPECIAL PROTECTION INFORMATION) *****

VENTILATION: USE ONLY IN A CHEMICAL FUME HOOD.

FIGHTING: SELF-CONTAINED BREATHING APPARATUS SHOULD BE USED WHEN FIGHTING FIRES INVOLVING A CHEMICAL.

ING: PROTECTIVE CLOTHING

GLOVES: COMPATIBLE CHEMICAL-RESISTANT GLOVES

EYE PROTECTION: CHEMICAL SAFETY GOGGLES

RESPIRATORY PROTECTION: NIOSH/MSHA-APPROVED RESPIRATOR

ADDITIONAL PROTECTION: SAFETY SHOWER AND EYE BATH

***** SECTION IX (STORAGE AND HANDLING PRECAUTIONS) *****

SPECIAL PRECAUTIONS: TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
POSSIBLE RISK OF IRREVERSIBLE EFFECTS. WEAR SUITABLE
PROTECTIVE CLOTHING. DO NOT BREATHE DUST. POSSIBLE
TERATOGEN.

***** SECTION X (TRANSPORTATION AND SHIPPING REQUIREMENTS) *****

THE FOLLOWING LABEL AND SHIPPING INFORMATION IS REQUIRED BY THE U.S.
DEPARTMENT OF TRANSPORTATION WHENEVER THIS PRODUCT IS OFFERED FOR
TRANSPORTATION:

D.O.T. HAZARD CLASS: NOT LISTED

D.O.T. DESCRIPTION: NOT LISTED

D.O.T. DESCRIPTION: NOT LISTED

DESCRIPTION: NOT LISTED

UN NO.: NOT LISTED

LABEL REQUIRED: NOT LISTED

Exhibit B
MSDS - Drug Product

MATERIAL SAFETY DATA INFORMATION

16-JUN-1995

***** SECTION I *****

MANUFACTURER/SOURCE OF INFORMATION: ALCON LABORATORIES, INC.
EMERGENCY TEL: 817-551-4444
ADDRESS: 6201 SOUTH FREEWAY, FORT WORTH, TEXAS 76134

CHEMICAL NAME AND SYNONYMS:
DICLOFENAC 0.1% OPHTHALMIC SOLUTION;

CAS NO.: AP0001035

PRODUCT CODE:

FDA/NDA NO.:

OSHA HAZARD RATINGS (SCALE 0-3):

HEALTH-N/A

FIRE-N/A

REACTIVITY-N/A

PERSISTENCE-N/A

***** SECTION II (COMPONENTS AND CONTAMINANTS) *****

PERCENTAGE:

COMPONENT:

DICLOFENAC SODIUM, NOC

AL06778, NOC

MANNITOL, USP

TROMETHAMINE, USP, AR

BORIC ACID, NF

POLYQUATERNIUM-1, NOC

HYDROXYPROPYL METHYLCELLULOSE (2910) (E4M), USP

HYDROCHLORIC ACID, NF AND/OR

SODIUM HYDROXIDE, NF

PURIFIED WATER, USP

FORMULATION PROPRIETARY: WE WILL MAKE THIS INFORMATION AVAILABLE TO MEDICAL PERSONNEL IN CASE OF AN EMERGENCY.

EXPOSURE LIMITS: NOT DETERMINED

***** SECTION III (PHYSICAL DATA) *****

HAZARD DESCRIPTION: CLEAR, PALE YELLOW, AQUEOUS SOLUTION

BOILING POINT: N/A

MELTING POINT: N/A

DENSITY: 1.0245 G/ML

VAPOR PRESSURE: N/A

EVAPORATION RATE: N/A

SOLUBILITY IN WATER: ALL COMPONENTS ARE WATER SOLUBLE.

VAPOR DENSITY: N/A

***** SECTION IV (FIRE AND EXPLOSION HAZARD DATA) *****

AND EXPLOSION HAZARD: THIS MATERIAL SHOULD NOT PRESENT A FIRE OR EXPLOSION HAZARD.

FLASH POINT: N/A

UPPER EXPLOSION LIMIT: N/A

LOWER EXPLOSION LIMIT: N/A

FIREFIGHTING MEDIA: USE EXTINGUISHING MEDIA APPROPRIATE FOR THE SURROUNDING FIRE CONDITIONS.

FIREFIGHTING: WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING.

TOXIC GASES PRODUCED: CARBON DIOXIDE, CARBON MONOXIDE, NITROGEN OXIDES

***** SECTION V (HEALTH EFFECTS AND FIRST AID) *****

TOXICITY: ORAL OR PARENTERAL CONTACT WITH HIGH CONCENTRATIONS OF ONE OR MORE OF THE COMPONENTS IN THIS FORMULATION MAY PRODUCE HYPERSENSITIVITY IN A SMALL NUMBER OF THE GENERAL POPULATION. AS THE CONCENTRATION OF THESE COMPONENTS IS RELATIVELY SMALL IN THE FINISHED PRODUCT, THIS FORMULATION SHOULD NOT PRESENT SIGNIFICANT CONTACT HAZARDS TO HUMANS.

PRECAUTIONS TO CONSIDER: FOLLOW DIRECTIONS FOR INTENDED USE.

INDIVIDUALS DEVELOPING HYPERSENSITIVITY REACTIONS (ANAPHYLAXIS) MUST RECEIVE IMMEDIATE MEDICAL ATTENTION. AS A GENERAL RULE, INDIVIDUALS WORKING WITH CHEMICALS SHOULD CONSIDER ALL CHEMICALS TO BE POTENTIALLY HAZARDOUS EVEN IF THEIR INDIVIDUAL HAZARDS ARE UNCHARACTERIZED OR UNKNOWN.

CARCINOGENICITY: CARCINOGENICITY STUDIES IN RATS ADMINISTERED DICLOFENAC SODIUM ORALLY UP TO 2 MG/KG/DAY REVEALED NO SIGNIFICANT INCREASES IN TUMOR INCIDENCE. THERE WAS A SLIGHT INCREASE IN BENIGN RAT MAMMARY FIBROADENOMAS AMONG FEMALES IN THE MID-DOSE GROUP, BUT THE INCREASE WAS NOT SIGNIFICANT FOR THIS COMMON RAT TUMOR. A TWO-YEAR CARCINOGENICITY STUDY IN MICE AT ORAL DOSES UP TO 2 MG/KG/DAY OF DICLOFENAC SODIUM DID NOT REVEAL ANY ONCOGENIC POTENTIAL.

INHALATION--

ACUTE EXPOSURE: MAY CAUSE IRRITATION TO THE NASAL MUCOSA AND RESPIRATORY TRACT SHOULD INSUFFLATION OF PRODUCT OCCUR.

CHRONIC EXPOSURE: NOT DETERMINED

FIRST AID: REMOVE TO FRESH AIR. IF NOT BREATHING, PERFORM ARTIFICIAL RESPIRATION. OBTAIN APPROPRIATE MEDICAL ATTENTION.

CONTACT--

SKIN EXPOSURE: THIS PRODUCT CONFORMS TO FDA REGULATIONS AND GUIDELINES

FOR AN OPHTHALMIC DRUG AND THUS IT IS NOT EXPECTED TO PRESENT A DERMAL IRRITATION POTENTIAL.

.CHRONIC EXPOSURE: NOT DETERMINED

.FIRST AID: IF IRRITATION OCCURS, FLUSH SKIN WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. IN THE EVENT OF ANY ADVERSE EFFECTS, OBTAIN APPROPRIATE MEDICAL ATTENTION.

YE CONTACT--

.ACUTE EXPOSURE: NOT DETERMINED

.CHRONIC EXPOSURE: NOT DETERMINED

.FIRST AID: IF IRRITATION OCCURS, IMMEDIATELY FLUSH EYES WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. IN THE EVENT OF ANY ADVERSE EFFECTS, OBTAIN APPROPRIATE MEDICAL ATTENTION.

NGESTION--

.ACUTE EXPOSURE: ORAL LD50: MOUSE-125 MG/KG
ORAL LD50: RAT-53 MG/KG

.CHRONIC EXPOSURE: SEE CARCINOGENICITY SECTION.

.FIRST AID: WASH OUT MOUTH WITH WATER. IN THE EVENT OF ANY ADVERSE EFFECTS, OBTAIN APPROPRIATE MEDICAL ATTENTION.

***** SECTION VI (REACTIVITY DATA) *****

REACTIVITY: STABLE

COMPATIBILITIES: NONE OTHER THAN WATER ALONE WOULD PRODUCE.

COMPOSITION: WHEN HEATED TO DECOMPOSITION, MATERIAL EMITS TOXIC FUMES.

POLYMERIZATION: WILL NOT OCCUR

CONDITION TO AVOID: NONE KNOWN

***** SECTION VII (SPILL OR LEAK PROCEDURES) *****

SPILL: WEAR APPROVED RESPIRATOR AND CHEMICALLY COMPATIBLE GLOVES. VACUUM OR SWEEP UP SPILLAGE. PLACE SPILLAGE IN APPROPRIATE CONTAINER FOR WASTE DISPOSAL. VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

DISPOSAL: DISPOSE IN ACCORDANCE WITH ALL APPLICABLE FEDERAL, STATE AND LOCAL ENVIRONMENTAL REGULATIONS. THIS PRODUCT DOES NOT MEET THE DEFINITION OF HAZARDOUS WASTE AS DEFINED IN 40CFR, PART 261.11.

***** SECTION VIII (SPECIAL PROTECTION INFORMATION) *****

THE FOLLOWING INFORMATION ASSUMES LARGE QUANTITIES OF THE PRODUCT SUCH AS MIGHT BE ENCOUNTERED IN WAREHOUSE STORAGE OR AN INDUSTRIAL ACCIDENT.

VENTILATION: USE GENERAL OR LOCAL EXHAUST

FIREFIGHTING: SELF-CONTAINED BREATHING APPARATUS SHOULD BE USED WHEN FIGHTING FIRES INVOLVING A CHEMICAL.

CLOTHING: APPROPRIATE LABORATORY APPAREL, PROTECT EXPOSED SKIN.

GLOVES: RUBBER

EYE PROTECTION: SAFETY GOGGLES

RESPIRATORY PROTECTION: NIOSH/MSHA-APPROVED

***** SECTION IX (STORAGE AND HANDLING PRECAUTIONS) *****

SPECIAL PRECAUTIONS: STORE IN A TIGHT CONTAINER AS DEFINED IN THE UNITED STATES PHARMACOPEIA. THIS MATERIAL SHOULD BE HANDLED AND STORED PER LABEL AND OTHER INSTRUCTIONS TO ENSURE PRODUCT INTEGRITY.

PRECAUTIONS: AVOID BREATHING DUST OR MIST. USE WITH ADEQUATE DUST CONTROL. WASH THOROUGHLY AFTER HANDLING. DO NOT PERMIT EATING, DRINKING OR SMOKING NEAR MATERIAL.

***** SECTION X (TRANSPORTATION AND SHIPPING REQUIREMENTS) *****

THIS PRODUCT DOES NOT POSE AN UNREASONABLE RISK TO HEALTH AND SAFETY OR PROPERTY WHEN TRANSPORTED IN COMMERCE. THE HAZARD CLASS DEFINITIONS OF 49CFR, PART 173 ARE NOT APPLICABLE TO THIS PRODUCT.

THE INFORMATION CONTAINED HEREIN IS FURNISHED WITHOUT WARRANTY OF ANY KIND. THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE ALL INCLUSIVE AND SHOULD BE USED ONLY AS A GUIDE. USERS SHOULD MAKE INDEPENDENT DETERMINATIONS OF THE SUITABILITY AND COMPLETENESS OF INFORMATION FROM ALL SOURCES TO ASSURE PROPER USE AND DISPOSAL OF THESE MATERIALS AND THE SAFETY AND HEALTH OF EMPLOYEES AND CUSTOMERS.

APPROVED:

R&D: E.D./J.H./R.J./T.K.

DATE: 6/16/95

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