CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-600

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Tazarotene 0.05%, 0.1% Gel

NDA 20-600

Division of Dermatologic and Dental Drug Products (HFD-540)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

Tazarotene 0.05%, 0.1% Gel

NDA 20-600

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 tazarotene, Allergan, Inc., has prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a(b)(3) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Tazarotene is a chemically synthesized drug which is administered as a 0.01% topical gel in the treatment for acne and psoriasis. The drug substance is manufactured by contract pharmaceutical manufacturers. The drug product is made by Allergan, Inc. in California. The finished drug product will be used in hospitals, clinics and patients in their homes throughout the United States.

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 high temperature incinerator or by licensed landfill. 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 Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of 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. 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.

10/31/96 P G Vincent
DATE

Prepared by
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

10/31/96 Nancy B. Sager
DATE

Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

HFD-540/FCross copy to NDA 20-600
HFD-357/FONSI File 20600
HFD-357/Docket File
HFD-205/FOI COPY

ENVIRONMENTAL ASSESSMENT

PURSUANT TO 21 CFR 25.31

Trade name ™ (tazarotene) 0.05%, 0.1%, Gel
NDA 20-600

1. **DATE:** October 10, 1996 Revision 1
   August 30, 1995 Revision 0

2. **NAME OF APPLICANT**

   Allergan

3. **ADDRESS:**

   2525 Dupont Drive
   Irvine, California 92715

4. **DESCRIPTION OF PROPOSED ACTION:**

   a. Requested Approval

   A New Drug Application (NDA 20-600) has been submitted to the Food and Drug Administration requesting approval of manufacture of the prescription topical product Trade name ™ (tazarotene) 0.05%, 0.1%, Gel (hereinafter referred to as "the Product") at Allergan, Inc., 8301 Mars Drive, P.O. Box 2675, Waco, Texas 76712. Allergan, Inc. is proposing to manufacture, fill and package the Product at its facility in Waco, Texas.

   b. Need for Action

   The Product is intended for use in humans under the prescription of a licensed physician. The Product will be used as a safe and effective treatment for acne and psoriasis.

   c. Production Locations

   This Environmental Assessment is prepared pursuant to Title 21 CFR 25.31(a) and is intended to cover the manufacture of the Product which contains the active ingredient AGN 190168.

   Affirmations of compliance with environmental, health and safety regulations from the active ingredient manufacturers are included in Confidential Appendices II and III.

The environment adjacent to, and present at, the active ingredient manufacturers facilities is light industrial, commercial, residential and rural in nature. The environment adjacent to, and present at, the Allergan, Inc. facility is light industrial, residential and rural in nature.

d. Locations of Use

The locations of use will be hospitals, clinics and patients in their homes. The environment at Allergan's customer locations is widespread and the nature is diverse.

e. Disposal Sites

Returned Goods are sent by the customer to the Allergan facility located at 8301 Mars Drive, P.O. Box 2675, Waco, Texas, 76712 per Allergan's Policy which is included in Confidential Appendix V. The Allergan facility located in Waco disposes of returned goods using Laidlaw Environmental Services, Inc. located at 500 Battleground Road, La Porte, Texas 77571. Returned goods are either incinerated or buried if they cannot be resold. Disposal facility details are found in Confidential Appendix V.

The Allergan Waco facility disposes of rejected, expired or off-specification batches, ingredients, and sub-components of a batch by high temperature incineration or by land disposal at an industrial landfill which are licensed by the EPA or an appropriate state authority to destroy hazardous materials. Laidlaw Environmental Services, Inc. located at 500 Battleground Road, La Porte, Texas 77571 provides this service for the Allergan Waco facility. Disposal facility details are found in Confidential Appendix V.

Manufacturing disposal are described in section 6.b. "Controls Exercised".

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

a. Nomenclature

i. Established Name (U.S. Adopted Name - USAN)

Tazarotene

ii. Brand/Proprietary Name

Tazarotene

iii. Chemical Names

Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate

Allergan Code Number (AGN #)

AGN 190168 (Formerly SK&F 190168)

Other Names

Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate
Ethyl 6-[(3,4-dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl]-3-pyridinecarboxylate

b. **Chemical Abstract Services Number**

118292-40-3

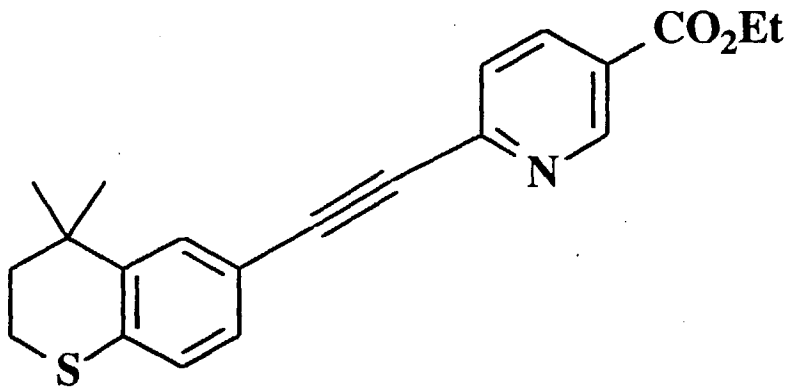
c. **Molecular Formula**

$C_{21}H_{21}NO_2S$

d. **Molecular Weight**

351.46

e. **Structural Formula**



f. **Physical Description**

Yellow powder or crystals

Melting Range

103-106°C

pK_a Value

1.5

Partition Coefficient

Octanol/water log P of AGN 190168 = 4.3

This value was determined at room temperature. The aqueous phase was buffered to pH 7.4.

g. **Additives**

The Product will be marketed as 3.5 g, 10 g, 30 g and 100 g units containing the active ingredient AGN 190168 in concentrations of 0.1% w/w and 0.05% w/w, with the following inactive ingredients:

Chemical Name	*Molecular Formula*	*Molecular Weight*	*CAS Number*
Edetate Disodium, USP/EP	$C_{10}H_{14}N_2Na_2O_8$	336.21	139-33-3
Ascorbic Acid, USP/EP	$C_6H_8O_6$	176.14	50-81-7
Poloxamer 407, NF (meets the Poloxamer monograph requirements)	$HO(C_2H_4O)_{101}(C_3H_6O)_{56}(C_2H_4O)_{101}H$	9,840 to 14,600	9003-11-6
Hexylene glycol, NF	$C_6H_{14}O_2$	118.18	107-41-5
Carbomer 974P, NF/BP (meets the carbomer 934 monograph requirements)			
Tromethamine, USP	$C_4H_{11}NO_3$	121.14	77-86-1
Polyethylene glycol 400, NF/IP	$H(OC_2H_4)_nOH$ n = 8.2 to 9.1	380 to 420	25322-68-3
Polysorbate 40, NF	Palmitate ester of sorbitol and its anhydrides copolymerized with ethylene oxide	varies	9005-66-7
Butylated Hydroxyanisole, NF/EP	$C_{11}H_{16}O_2$	180.25	25013-16-5

Butylated Hydroxytoluene, NF/EP	$C_{15}H_{24}O$	220.36	128-37-0
Benzyl Alcohol, NF/EP	C_7H_8O	108.14	100-51-6
Purified Water	H_2O	18	

The chemical and physical data for the inactive ingredients are found in Confidential Appendix V. The material safety data sheets (MSDS) for the active ingredient AGN 190168 and Trade name ™ (tazarotene) 0.05%, 0.1%, Gel are found in Non-confidential Appendix I. The manufacturing process including the waste generation points of the active ingredient manufacturers are included in Confidential Appendices II and III.

h. Impurities

There are no impurities found in the drug substance at levels greater than 1%.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

a. Substances Expected to be Emitted

At the active ingredient manufacturing facilities, the active ingredient AGN 190168 will be produced by organic synthesis reactions in batch operations in accordance with FDA requirements. Tazarotene will be manufactured by the two contract synthesis facilities identified in Confidential Appendices II and III. Typical organic synthesis reactions are performed in the plant. These employ organic and/or inorganic solvents as carrying agents to which are added any number of reactants. Most products are isolated in solid form as is the case with AGN 190168, via crystallization or precipitation. These are then dried and packaged. A small percentage of the products are isolated as a liquid, typically by distillation. The specific chemicals used in the synthesis reactions and the potential environmental emissions are listed in Confidential Appendix II and III.

During the production of the Product at the Allergan facility in Waco, the following substances are expected to be introduced into the environment: off-specification Product, off-specification components or ingredients, HEPA air filters used in maintaining the particle levels in the manufacturing areas and/or cleaning residuals from Product manufacture. Also, the quality control laboratories will generate laboratory waste chemicals. The specific chemicals used in the manufacture of the Product are listed in Item 5.g. above and the potential environmental emissions are included in Confidential Appendix V.

The estimated number of units that will be produced for distribution on an annual basis at the Allergan, Inc. facility is included in the EIC calculations in Confidential Appendix V. The estimated quantity of active ingredient that will be

used annually to produce the Product is included in the EIC calculations in Confidential Appendix V. This assumes the worst case in that all the Product will be at a concentration of 0.1% active ingredient. The amount of active ingredient used annually will decrease depending on the unit quantity of the 0.05% active ingredient concentration gel produced which makes up part of the total units produced annually. The exact number of units has not been determined.

The Product is distributed evenly across the U.S. as well as other countries. It is assumed that the customers will dispose of the tubes after use in the local trash collection system which will either recycle the tubes or send them for disposal.

b. Controls Exercised

At the active ingredient manufacturing facilities, although not expected, residual (very insignificant) amounts of the manufacturing substances may enter the environment at the sites of production as the result of equipment and facilities cleaning. However, because of the high cost of pharmaceutical materials, as well as Good Manufacturing Practices (GMP) provisions requiring strict accounting of their use, the manufacturing process is expected to result in minimal residual releases to the environment. Solvents are captured using condensers. The solvents are either recycled or disposed via incineration. Filters are used to capture the active ingredient as solids. Confidential Appendices II and III contain the permits, process flow diagrams with emission points and an environmental assessment of each facility.

At the Allergan, Inc. facility, although not expected, residual (very insignificant) amounts of the manufacturing substances may enter the environment at the sites of production as the result of equipment and facilities cleaning. However, because of the high cost of pharmaceutical materials, as well as Good Manufacturing Practices (GMP) provisions requiring strict accounting of their use, the manufacturing process is expected to result in minimal residual releases to the environment.

Any residuals (gel or cleaning residues) in washwaters are pH adjusted, passed through a grease trap and discharged to the Brazos River Authority's treatment facility which is permitted by the Texas Natural Resources Conservation Committee (formerly the Texas Water Commission) and the U.S. Environmental Protection Agency. Chemicals such as laboratory chemicals which cannot be recycled or reused are sent offsite for proper disposal. The solid waste disposal contractor is Laidlaw Environmental Services, Inc. located at 500 Battleground Road, La Porte, Texas 77571. The facility does not require any air permits. The HEPA air filters used to filter the air in the manufacturing areas are 99.9% efficient. The filters will be disposed as solid waste at an industrial landfill. Confidential Appendix V contains the permits associated with environmental controls.

c. Citation of and Statement of Compliance with Emission Requirements

The active ingredient manufacturers are in compliance with all applicable federal, provincial and local environmental, health and safety regulations. Allergan, Inc. at Waco, Texas is in compliance with all applicable federal (OSHA, EPA), state and local environmental, health and safety regulations. Confidential Appendices II, III and V include the statements of compliance, and applicable permits and regulations for each facility.

It is assumed that the customers of the finished Product operate in compliance with applicable federal, state and local environmental, health and safety regulations.

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

Approval of this New Drug Application for the Product will have no significant adverse effects on compliance with applicable regulations. The manufacture of the Product will not impact compliance with the waste water discharge permit. The solid waste impact is expected to be minimal with at worst case a 6.6% increase in solid waste generation and insignificant impact (< 1%) in hazardous waste generation.

e. Expected Introduction Concentrations

i. Expected Introduction Concentration from Use

Since this is a topical gel, insignificant emissions to the air or discharges to wastewater result from the patient's use of the drug product. There are also insignificant waste impacts anticipated from the patient's use. The patient use EIC - Aquatic (ppm) is 1.376×10^{-6} ppm of AGN 190168. The calculations are included in Confidential Appendix V.

ii. Expected Introduction Concentration from Disposal

In the manufacture of the active ingredient AGN 190168, the quantity entering the environment from the manufacturing process is negligible. In the manufacture of the Product, the quantity entering the environment from the manufacturing process is negligible. The EIC calculations are included in Confidential Appendix V.

7, 8, 9, 10, and 11

The Product is a pharmaceutical gel for topical administration. Items 7 through 11 therefore are not required per 21 CFR Section 25.31a(b)(3).

12. LIST OF PREPARER(S):

Paul A. Gutsch, Ph.D.
Vice President - Operations
Cambridge Chemical, Inc.

Mr. Geoff Evans, P. Eng.
Manager, Technical Operations
Torcan Chemical, Ltd.

Michael Whaley, REA
Director
Environmental Health

Please refer to Confidential Appendix IV for the curriculum vitae of the preparers.

PERSONS AND AGENCIES CONSULTED:

Nancy Sager, CDER, FDA

13. CERTIFICATION

The undersigned official certifies that the information presented in this report is true, accurate, and complete to the best of the knowledge of Allergan, Inc.

Michael Whaley

ALLERGAN, INC.
Michael Whaley
Director
Environmental Health

Date: October 10, 1996

14. REFERENCES

Guidance for Industry For the Submission of an Environmental Assessment in Human Drug Applications and Supplements, CDER, November 1995

15. APPENDICES

Non-confidential Appendix I - AGN 190168 MSDS and Trade name ™ (tazarotene) 0.05%, 0.1%, Gel MSDS

Confidential Appendix II - Supplements

- Synthesis Description and Process flow diagram with emission points
- Estimated Process Loss Calculations
- Listing of the EHS regulations applicable to the facility
- Environmental,Health and Safety Compliance Certification Statement
- Facility Layout

Confidential Appendix III - Supplements

- Environmental Assessment including the Environmental, Health and Safety Compliance Certification Statement
- Synthesis Description and Process flow diagram with emission points
- Estimated Process Loss Calculations
- Listing of the EHS regulations applicable to the facility

Confidential Appendix IV - Curriculum Vitae of the Preparers

Confidential Appendix V - Allergan Waco Supplements

- Facility Layout
- EPA identification number for hazardous waste generation
- Wastewater discharge permit number
- Listing of the EHS regulations applicable to the facility
- Trade name ™ (tazarotene) 0.05%, 0.1%, Gel Manufacturing Schematic
- Estimated Process Loss Calculations
- EIC calculations
- Chemical structural and molecular formulas and physical appearance
- Policy on Returned Goods

NON-CONFIDENTIAL APPENDIX I

ALLERGAN, INC.
MATERIAL SAFETY DATA SHEET

National Fire Protection Association (NFPA) Rating: Health: 3 Flammability: 0 Reactivity: 0 Special: 0

PRODUCT IDENTIFICATION

Compound Name:	**TAZAROTENE BULK DRUG (AGN 190168 BULK DRUG SUBSTANCE)**
Chemical Class:	Polyaromatic Retinoid
Manufacturer's Name:	Allergan, Inc.
Address:	2525 Dupont Drive Irvine, CA 92612
24-Hr. Phone Number	Allergan, Inc. 714-246-4335
Phone Number between 8 am-5 pm Pacific Time M-F	714-246-5940
Date Revised:	July 26, 1996

HAZARDOUS INGREDIENTS

Chemical Name	CAS Number	Percent (by weight)	Exposure Limits in Air ACGIH - TLV
Tazarotene (AGN 190168	118282-40-3	100%	None Established

HAZARDS IDENTIFICATION AND FIRST AID

Emergency Overview: **Contact with the skin can cause irritation, reddness, swelling, and peeling of the skin.** This compound class affects many different components of the human body including the retina, epithelial tissue, bone, reproductive systems and the immune system. **PREGNANT OR NURSING WOMEN AS WELL AS WOMEN OF CHILDBEARING AGE SHOULD STRICTLY OBSERVE ALL PRECAUTIONS FOR SAFE HANDLING AND PROTECTIVE EQUIPMENT USE DESCRIBED IN THIS DOCUMENT WHEN WORKING WITH THIS MATERIAL.**

HAZARDS IDENTIFICATION AND FIRST AID (Continued)

Primary Routes of Entry into the Body:	Inhalation, skin and eye contact
Potential Health Effects	Contact with this minor quantities of this product may produce skin dryness, itching, reddness, peeling or burning. Other potential health effects listed in this MSDS are based on known effects caused by other retinoid compounds. Overexposure to members of this class of compounds may affect liver function causing hypertriglyceridemia. Other symptoms may include conjunctival irritation, hair loss, headache, edema, fatigue, dermatitis, nausea and visual disturbances.
Reproductive Effects:	Adverse reproductive outcomes, specifically spontaneous fetal abortions or malformed fetal development, have been reported among women who were administered therapeutic doses (orally) of Retinoids. Therefore, **Women of childbearing age should strictly observe all precautions for safe handling and protective equipment use described in this MSDS when handling this material.**
Carcinogenicity	None of the components of this product are listed as carcinogens by the NTP, IARC or OSHA. In long-term studies, no increased rates of tumor formation were observed in mice or rats.
Emergency First Aid Procedures:	
Eye Contact:	Immediately flush eyes with water for 15 minutes. Obtain medical attention.
Skin Contact:	Immediately flush skin with water for 15 minutes. Remove contaminated clothing and shoes. Wash contaminated clothing before reuse. Destroy or thoroughly clean contaminated shoes. Get medical attention if symptoms are present.
Inhalation:	Move to fresh air. If symptoms occur, obtain medical attention. Treat symptomatically.
Ingestion:	Consult a physician or poison control center immediately.

FIRE FIGHTING MEASURES

Flash Point °F (Seta Flash Cup):	No data for this product
Autoignition Temperature:	No data for this product
Fire-Extinguishing Materials:	Water fog, CO_2, foam or dry chemical
Specific Firefighting Procedures:	Use self-contained breathing apparatus in enclosed or confined spaces or as otherwise needed.
Unusual Fire and Explosion Hazards:	None known

SAFE HANDLING MEASURES

Steps to be Taken if Material is Spilled or Released	Use wet methods or HEPA vacuum to remove solids. Do not sweep or use other method which generates dust. Flush spill area with water.
Waste Disposal Methods:	This product is not classified as a hazardous waste when disposed of. Disposal in a properly permitted hazardous waste incinerator or industrial landfill is recommended.
Precautions to be Taken in Handling and Storage:	This material is sensitive to sunlight, air and oxygen.

EXPOSURE CONTROL

Engineering Controls:	This material should be handled in a glove box, laboratory fume hood or in other areas equipped with local exhaust ventilation capable of preventing dust emissions.
Respiratory Protection:	This material does not have established exposure limits. If dust control ventilation systems are not present when handling this compound, wear an approved air-purifying respirator for dusts and mists when working with small quantities (milligrams). For larger quantities (grams), or where dust generation is likely, wear a full-face or hooded HEPA-equipped powered air-purifying respirator or a positive pressure air-supplied hood.

Eye and Face Protection:	When handling small quantities, wear safety glasses with side shields (or goggles) and a face shield. For larger quantities or where dust generation is likely, wear respiratory protection incorporating eye and face protection (full-face or hood).
Protective Clothing:	Wear Rubber (latex) or other chemical-resistant gloves when handling Tazarotene Bulk Drug Substance. For small quantities, wear lab coat or other protective clothing. For large quantities or where dust generation is likely, use disposable coveralls with taped seams or full encapsulating suit.
Hygienic Work Practices:	Do not allow contact of contaminated gloves or hands with skin surfaces. Wash hands thoroughly after handling. No eating, drinking or smoking in area. Thoroughly clean or dispose of any contaminated protective equipment.

PHYSICAL AND CHEMICAL PROPERTIES

Vapor Density (Air = 1):	Not applicable (solid)
Specific Gravity:	No data for this product
Vapor Pressure (mm Hg at 20° C):	No data for this product
Melting Point:	105 °C
Appearance:	Light yellow solid

REACTIVITY DATA

Stability:	Stable
Materials to Avoid:	Store away from oxidizers and heat.
Hazardous Polymerization:	None known
Hazardous Decomposition Products:	None known

TOXICOLOGICAL INFORMATION

The dosages listed refer to quantities of the active ingredient Tazarotene (AGN 190168) administered.

SKIN: Daily dermal application of up to 0.5 mg/kg/day for 3 months and 0.25 mg/kg/day for 12 months to the skin of Hanford miniswine produced no evidence of systemic toxicity. Skin response was dose dependent with minimal to moderate to marked irritation occurring as the dose increase from 0.05 to 0.5 mg/kg/day. Black scabs formed after four weeks of the study with dosages higher than 0.05 mg/kg. Twice daily dermal application (0.05 mL/application) of concentrations 0.01% to 0.1% to rats for six months produced treatment-related irritation which increased in intensity and frequency with concentration and duration of treatment. All skin reactions were observed to be reversible.

ORAL: A single oral dose of 2 g/kg to rats produced no lethality.

Doses in female rats of 2 mg/kg/day and in monkeys of 1.0-1.6 mg/kg/day for three months produced debilitation and/or death. Decreased hematological parameters, increased alkaline phosphates, AST and BUN and decreased total protein, calcium, cholesterol and albumin were observed. Many of the changes observed during the treatment period (fatty changes in the liver, decreased hemoglobin, increased AST) are similar to those seen during hypervitaminosis A. During the recovery period, these changes reversed to normal. At higher doses, a reduction of body weight gain, hepatic impairment and bone effects were observed. These effects are similar to those observed for other retinoid compounds, and were reversible after cessation of treatment.

In a three month study in monkeys, doses of 0.25 mg/kg produced no significant adverse effects. A dose level of 1.6 mg/kg produced renal failure and mineralization of various soft tissues. No blood cell or blood chemistry abnormalities were observed at any dose level. At high dose levels administered for six months or longer, skeletal abnormalities similar to those observed with other retinoid compounds, including the disruption and closure of the growth plate, ankylosis of the vertebrae, and deformity of the joints were observed.

REPRODUCTION: Dermal administration of this compound to rats and rabbits produced no evidence of teratogenicity, impaired fertility or reproductive capabilities in the test animals or of adverse effects in their offspring. Developmental toxicity was observed in male offspring of treated female rats, characterized by decreased lactation pup weights (0.05 to 0.125 mg/kg/day dosage).

Oral administration of this material to rats and rabbits at doses of 0.20 mg/kg/day (rabbits) and 0.25 mg/kg/day (rats) resulted in developmental toxicity. A no effect level of 0.05 mg/kg/day was established. Similar teratogenic effects have been reported for other retinoid compounds.

CARCINOGENICITY: No increased tumorgenicity was observed in mice following dermal application of this compound at dosages of up to 1.0 mg/kg/day for 21 months. Dietary

administration of this material to rats at dosages of up to 0.125 mg/kg/day for two years resulted in no increased tumorgenicity.

MUTAGENICITY: This compound was found to be non-mutagenic in the Ames Salmonella assay (with and without metabolic activation), did not produce structural chromosomal aberrations in a human lymphocyte assay, and was non-mutagenic in the CHO/HPRT mammalian cell forward gene mutation assay.

PHOTOSENSITIVITY: This compound was determined to be non-photosensitizing and non-phototoxic in guinea pigs. In hairless mice, enhancement of photocarcinogenicity was observed in all treatment groups. Similar photocarcinogenic enhancement has been previously demonstrated for other retinoids (e.g. all-trans-retinoic acid).

The preceding information is based on available data and is believed to be correct. However, no warranty is expressed or to be implied regarding the accuracy of this information, the results to be obtained from the use thereof or the hazards connected with the use of the material. Since the information contained herein may be applied under conditions beyond our control and with which we may be unfamiliar, Allergan does not assume any responsibility for the results of its use. This information is furnished upon the condition that the persons receiving it shall make their own determinations of the effects, properties, and protections which pertain to their particular conditions.

ALLERGAN INC.
MATERIAL SAFETY DATA SHEET

National Fire Protection Association (NFPA) Rating: Health: 2 Flammability: 0 Reactivity: 0 Special: 0

PRODUCT IDENTIFICATION

Compound Name:	**TAZAROTENE GEL, 0.05% AND 0.1%** **(AGN 190168 GEL)**
Chemical Class:	Polyaromatic Retinoid
Manufacturer's Name:	Allergan, Inc.
Address:	2525 Dupont Drive Irvine, CA 92612
24-Hr. Phone Number	Allergan, Inc. 714-246-4335
Phone Number between 8 am-5 pm Pacific Time M-F	714-246-5940
Date Revised:	July 26, 1996

HAZARDOUS INGREDIENTS

Chemical Name	CAS Number	Percent (by weight)	Exposure Limits in Air ACGIH - TLV
Tazarotene (AGN 190168)	118292-40-3	<1%	None established
Hexylene Glycol	107-41-5	2%	25 ppm Ceiling
Benzyl Alcohol	100-51-6	1%	None established

HAZARDS IDENTIFICATION AND FIRST AID

Emergency Overview: May cause skin irritation with reddness and skin peeling on repeated or prolonged contact. When administered at therapeutic doses, certain retinoid compounds have been shown to cause adverse reproductive effects when administered during pregnancy. Women of child bearing age should strictly observe all precautions for safe handling and protective equipment use described in this document when handling this product.

HAZARDS IDENTIFICATION AND FIRST AID (Continued)

Primary Routes of Entry Into the Body:	Skin and eye contact
Potential Health Effects	In sensitive individuals, repeated or prolonged skin contact with Tazarotene Gel may result in skin dryness, itching, reddness, peeling or burning. Other potential health effects listed in this MSDS are based on known effects caused by other retinoid compounds. Overexposure to members of this class of compounds may affect liver function causing hypertriglyceridemia. Other symptoms may include conjunctival irritation, hair loss, headache, edema, fatigue, dermatitis, nausea and visual disturbances.
Reproductive Effects	Retinoids have been shown to produce an increased incidence of adverse reproductive outcomes, specifically spontaneous fetal abortions or malformed fetal development when orally administered to women during pregnancy. **Women of childbearing age should observe all precautions for safe handling and protective equipment use indicated in this MSDS when handling this product.**
Carcinogenicity	None of the components of this product are listed as carcinogens by the NTP, IARC or OSHA. In long-term studies, no increased rates of tumor formation were observed in mice or rats.
Emergency First Aid Procedures:	
Eye Contact:	Immediately flush eyes with water for 15 minutes. Obtain medical attention.
Skin Contact:	Tazarotene Gel is rapidly absorbed through the skin. Immediately flush skin with water for 15 minutes. Remove contaminated clothing and shoes. Wash contaminated clothing before reuse. Destroy or thoroughly clean contaminated shoes. Get medical attention if symptoms are present.
Inhalation:	Move to fresh air. If symptoms occur, obtain medical attention. Treat symptomatically.

Ingestion:	Consult a physician or poison control center immediately.

FIRE FIGHTING MEASURES

Flash Point °F (Seta Flash Cup):	>230° F (>110° C)
Autoignition Temperature:	786° F (419° C)
Fire-Extinguishing Materials:	Water fog, CO_2, foam or dry chemical
Specific Firefighting Procedures:	Use self-contained breathing apparatus in enclosed or confined spaces or as otherwise needed.
Unusual Fire and Explosion Hazards:	None known

SAFE HANDLING MEASURES

Steps to be Taken if Material is Spilled or Released:	Wipe up or take up with absorbent material. Do not allow contact with skin. Flush spill area with water.
Waste Disposal Methods:	This product is not a hazardous waste when disposed of. For small quantities, discard in a municipal landfil as ordinary trash. For large quantities, contact Allergan for information on return, recycle or disposal options.
Precautions to be Taken in Handling and Storage:	This material is sensitive to sunlight, air and oxygen.

EXPOSURE CONTROL

Engineering Controls:	None required during normal handling of Tazarotene Gel, 0.05 and 0.1%. In large quantities, Tazarotene Gel should be handled in a laboratory fume hood or in other areas equipped with suitable local exhaust ventilation.
Respiratory Protection:	None required during normal clinical administration of Tazarotene Gel. Gram quantities of the gel should be handled in well ventilated areas.

	For kilogram quantities, wear a powered air-purifying respirator or a positive pressure air-supplied respirator whenever local exhaust ventilation is not adequate.
Eye and Face Protection:	None required during normal administration or use of Tazarotene Gel. When handling gram quantities of the material, wear safety glasses with side shields (or goggles) or a full face shield.
Protective Clothing:	Rubber (latex) or other chemical-resistant gloves are recommended when administering or handling Tazarotene Gel. Wear lab coat or other protective clothing.
Hygienic Work Practices:	Avoid inadvertent contact with hands or face. Wash hands thoroughly after handling. No eating, drinking or smoking in area.

PHYSICAL AND CHEMICAL PROPERTIES

Vapor Density (Air = 1):	No data for this product
Specific Gravity (Water = 1.0 @ 20° C):	1.06
Vapor Pressure (mm Hg at 20° C):	No data for this product
Appearance:	Colorless to light yellow gel

REACTIVITY DATA

Stability:	Stable
Materials to Avoid:	Store away from oxidizers and heat.
Hazardous Polymerization:	None known
Hazardous Decomposition Products:	None known

TOXICOLOGICAL INFORMATION

The dosages listed refer to quantities of the active ingredient Tazarotene (AGN 190168) administered.

SKIN: Daily dermal application of up to 0.5 mg/kg/day for 3 months and 0.25 mg/kg/day for 12 months to the skin of Hanford miniswine produced no evidence of systemic toxicity. Skin response was dose dependent with minimal to moderate to marked irritation occurring as the dose increase from 0.05 to 0.5 mg/kg/day. Black scabs formed after four weeks of the study with dosages higher than 0.05 mg/kg. Twice daily dermal application (0.05 mL/application) of concentrations 0.01% to 0.1% to rats for six months produced treatment-related irritation which increased in intensity and frequency with concentration and duration of treatment. All skin reactions were observed to be reversible.

ORAL: A single oral dose of 2 g/kg to rats produced no lethality.

Doses in female rats of 2 mg/kg/day and in monkeys of 1.0-1.6 mg/kg/day for three months produced debilitation and/or death. Decreased hematological parameters, increased alkaline phosphates, AST and BUN and decreased total protein, calcium, cholesterol and albumin were observed. Many of the changes observed during the treatment period (fatty changes in the liver, decreased hemoglobin, increased AST) are similar to those seen during hypervitaminosis A. During the recovery period, these changes reversed to normal. At higher doses, a reduction of body weight gain, hepatic impairment and bone effects were observed. These effects are similar to those observed for other retinoid compounds, and were reversible after cessation of treatment.

In a three month study in monkeys, doses of 0.25 mg/kg produced no significant adverse effects. A dose level of 1.6 mg/kg produced renal failure and mineralization of various soft tissues. No blood cell or blood chemistry abnormalities were observed at any dose level. At high dose levels administered for six months or longer, skeletal abnormalities similar to those observed with other retinoid compounds, including the disruption and closure of the growth plate, ankylosis of the vertebrae, and deformity of the joints were observed.

REPRODUCTION: Dermal administration of this compound to rats and rabbits produced no evidence of teratogenicity, impaired fertility or reproductive capabilities in the test animals or of adverse effects in their offspring. Developmental toxicity was observed in male offspring of treated female rats, characterized by decreased lactation pup weights (0.05 to 0.125 mg/kg/day dosage).

Oral administration of this material to rats and rabbits at doses of 0.20 mg/kg/day (rabbits) and 0.25 mg/kg/day (rats) resulted in developmental toxicity. A no effect level of 0.05 mg/kg/day was established. Similar teratogenic effects have been reported for other retinoid compounds.

CARCINOGENICITY: No increased tumorgenicity was observed in mice following dermal application of this compound at dosages of up to 1.0 mg/kg/day for 21 months. Dietary

administration of this material to rats at dosages of up to 0.125 mg/kg/day for two years resulted in no increased tumorgenicity.

MUTAGENICITY: This compound was found to be non-mutagenic in the Ames Salmonella assay (with and without metabolic activation), did not produce structural chromosomal aberrations in a human lymphocyte assay, and was non-mutagenic in the CHO/HPRT mammalian cell forward gene mutation assay.

PHOTOSENSITIVITY: This compound was determined to be non-photosensitizing and non-phototoxic in guinea pigs. In hairless mice, enhancement of photocarcinogenicity was observed in all treatment groups. Similar photocarcinogenic enhancement has been previously demonstrated for other retinoids (e.g. all-trans-retinoic acid).

The preceding information is based on available data and is believed to be correct. However, no warranty is expressed or to be implied regarding the accuracy of this information, the results to be obtained from the use thereof or the hazards connected with the use of the material. Since the information contained herein may be applied under conditions beyond our control and with which we may be unfamiliar, Allergan does not assume any responsibility for the results of its use. This information is furnished upon the condition that the persons receiving it shall make their own determinations of the effects, properties, and protections which pertain to their particular conditions.