

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20763

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

**ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT**

FOR

NDA 20-763

NARATRIPTAN

Tablets 2.5 mg

Division of Neuropharmacological Drug Products

(HFD-120)

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

FINDING OF NO SIGNIFICANT IMPACT

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Division of Neuropharmacological Drug Products

(HFD-120)

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.

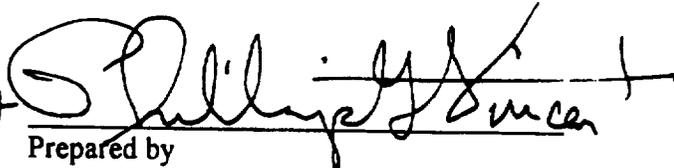
In support of their new drug application for NARATRIPTAN, Glaxo Wellcome Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) in the Tier 0 format which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

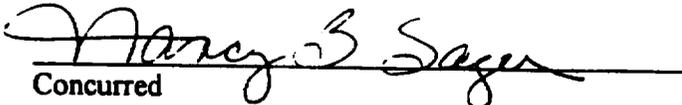
Naratriptan HCl is a chemically synthesized drug which is administered as a 2.5 mg tablet in the treatment of acute migraine. The drug substance is manufactured by Glaxo Wellcome Operations, Scotland, UK. Drug substance milling occurs at Glaxo Wellcome Operations, Dartford, England. Drug product tableting occurs at Glaxo Wellcome Operations, Hertfordshire, England. Drug product packaging occurs at Glaxo Wellcome Inc., Zebulon, NC. The finished drug product will be used in private residences throughout the US.

Naratriptan may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The projected environmental introduction concentration from use is less than 1 ppb. Therefore, the applicant has submitted a tier 0 EA without format items 7, 8, 9, 10 and 11 in accordance with the *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements, November 1995*.

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 expired drug product will be disposed of at a licensed incinerator. 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.

5/21/97 
DATE Prepared by
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

5/21/97 
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-120 /Lana Chen copy to NDA 20-763
HFD-357/FONSI File 20763
HFD-357/Docket File
HFD-205/FOI COPY

Appendix 1

Environmental Assessment

Naratriptan Tablets

ENVIRONMENTAL ASSESSMENT

Naratriptan Tablets

NDA-20-763

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1. DATE

November 15, 1996

2. APPLICANT

Glaxo Wellcome Inc.

3. ADDRESS

Five Moore Drive
Research Triangle Park, NC 27709

4. DESCRIPTION OF THE PROPOSED ACTION**4.a. Description of Requested Approval**

Glaxo Wellcome Inc. has filed an NDA pursuant to Section 505(b) of the Food, Drug and Cosmetic Act for Naratriptan Tablets. Naratriptan Tablets are supplied as 2.5 mg tablets in double foil blister packs with paper peel/push-through foil lidding or HDPE bottles with child resistant closures. This EA is being submitted pursuant to 21 CFR Part 25.31a(a).

4.b. Need for the Action

Naratriptan is a selective agonist for 5 hydroxytryptamine-1 (5HT₁) receptors mediating vascular contraction. The requested approval will allow Naratriptan to be marketed for the acute treatment of migraine attacks in adults.

4.c. Locations where Products will be Produced

The drug substance and all proprietary intermediates for Naratriptan will be manufactured in bulk at Glaxo Wellcome Operations in Montrose, Scotland. A milling stage will occur at Glaxo Wellcome Operations, Dartford. Tableting will occur at Glaxo Wellcome Operations in Ware with packaging at Glaxo Wellcome Inc., Zebulon, North Carolina.

The address of the Montrose facility is:

Glaxo Wellcome Operations
 10 Cobden Street
 Montrose
 Angus DD10 8EA
 Scotland, United Kingdom

The Montrose facility is located in the town of Montrose, a small town in northeast Scotland between the cities of Aberdeen and Dundee. The town is mainly residential and commercial with a small amount of industry. Industries in the town include agriculture, fishing and oil field supply services in addition to pharmaceutical manufacturing. The facility itself is located adjacent to the North Sea at the mouth of the South Esk River. The site covers 45 acres and is approximately one mile due east of the Montrose Basin. The site is bounded to the east by the local beach and the North Sea, to the south by the estuary of the South Esk river and to the north by residential, commercial and industrial properties.

The address of the Dartford facility is:

Glaxo Wellcome Operations
 Temple Hill
 Dartford
 Kent DA1 5AH
 England, United Kingdom

The Dartford facility covers about 135 acres and is located to the north of the town of Dartford. The town is mostly residential with a commercial core and peripheral services and light industry units. The area is an integral part of the Thames Corridor and is 18 miles downstream of the center of London. It is close to the Thames River Crossing which is part of the major motorway around London which links the three London International Air Terminals as well as the major roads into London from all parts of England. The facility is bounded to the south by the town of Dartford, to the east by a residential area, to the north by open pasture/marshland which leads to the River Thames and to the west by an industrial estate of varied service and light engineering units. It is close on its western borders to the tidal length of the River Darent which empties into the Thames at about a mile to the north of the site.

The address of the Ware facility is:

Glaxo Wellcome Operations
 Priory Street
 Ware -
 Hertfordshire SG12 0DJ
 England, United Kingdom

The Ware facility is located on the banks of the River Lea in Ware, a typical English market town about twenty miles north of London. The town, which covers 2.2 square miles, has an approximate population of 17,600. The Hertfordshire region enjoys an equable climate compared with many other counties of England. On average there are 175 days of rain in a year, 120 of which are classified as wet (greater than 1mm measured rain). The county is sufficiently far from the coast to experience on average only two days of gale force winds per year. The site is bounded to the north by residential and to the east and west by recreational with the River Lea Navigation to the south..

The address of the Zebulon facility is:

Glaxo Wellcome Inc.
 1011 North Arendell Street
 Zebulon, North Carolina 27597

The Zebulon facility is located about 25 miles east of Raleigh, North Carolina. The Town covers two square miles and has an approximate population of 2,889. The land use immediately adjacent to the production facility is commercial, with residential to the east and rural to the west, south and north. Other industries which are located in Zebulon include textile mills, metal finishers and a plastics manufacturer. The topography in Zebulon can be classified as flat to gently rolling. Elevations in the area generally between 250 and 350 feet above sea level. The area enjoys a favorable climate with minimum temperatures in winter seldom below 20°F and the summer maximum around 100°F. Annual precipitation in the area is approximately 42 inches. There are no National or State wilderness areas or parks in the vicinity of the Zebulon production facility. The site has a total of 224 acres. The Zebulon facility employs approximately 750 people.

4.d. Sites of Product Use

Naratriptan Tablets will be dispensed by pharmacies and used in private residences throughout the United States.

4.e. Sites of Disposal

Product that is introduced into the patient will be excreted in the urine and feces and distributed into wastewater treatment systems throughout the United States.

Returned and expired drug product is destroyed at the Glaxo Wellcome facility in Greenville, North Carolina. The facility is located northeast of the city of Greenville in Pitt County, North Carolina at the intersection of U.S. 13 North and State Road 1590. Pitt County is located in eastern North Carolina. The city of Greenville, with an estimated 1990 population of 48,000, is located in the center of the county approximately 50 kilometers southeast of Rocky Mount. Since the plant site is located in the coastal plain region of the state, terrain is extremely flat with terrain elevations changing only a few feet within a few kilometers of the plant site. The facility is located in an area zoned industrial. To the west-northwest of the facility the land is zoned Residential/Agricultural. The returned drug is destroyed by a controlled air incinerator which operates at temperatures ranging from 1200°F in the primary chamber to 1850°F in the secondary chamber. The incinerator operates under permit number 74-03-I issued by the N.C. Division of Solid Waste. The permit expires July 7, 1997. The address of the facility is:

Glaxo Wellcome Inc.
 Corner of U.S. 13/NC11 and State Road 1590
 Greenville, North Carolina 27834

5. IDENTIFICATION OF CHEMICAL SUBSTANCES

5.a Nomenclature

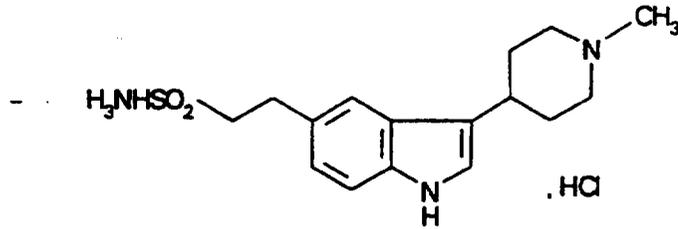
- | | | | |
|------|-------------------|---|--|
| i. | Established Name | - | naratriptan hydrochloride |
| ii. | Proprietary Name | - | Naratriptan |
| iii. | CAS Chemical Name | - | N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole
-5-ethanesulphonamide hydrochloride |

5.b CAS Number - 143388-64-1

5.c. Molecular Formula - $C_{17}H_{25}N_3O_2S.HCl$

5.d. Molecular Weight - 371.9

5.e Structural Formula



5.f Physical Description

Naratriptan hydrochloride is a white to pale yellow microcrystalline solid.

5.g Additives

Additives, including all excipient components and preservatives of the drug product, are as follows:

Excipient Name	CAS Number
Croscarmellose Sodium	NA
Lactose (anhydrous)	63-42-3
Magnesium Stearate	557-04-0
Microcrystalline cellulose	9004-34-6
Opadry® Green OY-S-21027	NA

5.h Impurities

The specifications for Naratriptan require that total impurity levels be no greater than 1.5% w/w. No single impurity will be above 0.3% w/w. As provided for in Section III.D.5.h. of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995), no specific impurities have been listed since any impurity present is at a level less than 1%.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.a. Substances Expected To Be Emitted

Drug Substance and Product Manufacturing

As provided for in Section VI of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995), certifications are provided for Glaxo Wellcome Operations in Montrose, Scotland where the drug substance, for Naratriptan will be manufactured in bulk and Glaxo Wellcome Operations in Dartford at which the drug substance will be milled and finally, Glaxo Wellcome Operations in Ware at which the tablets will be made. Attachments 1, 2, and 3 contain the certifications for Montrose, Dartford and Ware respectively.

Drug Product Packaging

Packaging of the Naratriptan Tablets will occur at the Glaxo Wellcome Inc. facility in Zebulon, North Carolina. There are no expected emissions from packaging procedures. The only solid waste generated is from packaging materials. Primary packaging materials will be completely destroyed by incineration at the Glaxo Wellcome incinerator in Greenville as described in 4.d.. Waste fiberboard over packing will be recycled.

6.b. Controls Exercised

Drug Substance and Product Manufacturing

As provided for in Section VI of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995), certifications are provided for Glaxo Wellcome Operations in Montrose, Scotland where the drug substance, for Naratriptan will be manufactured in bulk and Glaxo Wellcome Operations in Dartford at which the drug substance will be milled and finally, Glaxo Wellcome Operations in Ware at which the tablets will be made. Attachments 1, 2, and 3 contain the certifications for Montrose, Dartford and Ware respectively.

Drug Product Packaging

No description of the emission control equipment is necessary for the Glaxo Wellcome Inc. facility at Zebulon since no air or wastewater emissions will occur during the packaging of Naratriptan Tablets. However, any solid waste generated during packaging will be incinerated at the Glaxo Wellcome Greenville facility as discussed in section 4.d.

6.c. Citation And Statement Of Compliance With Emission Requirements

Drug Substance and Product Manufacturing

As provided for in Section VI of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995), certifications are provided for Glaxo Wellcome Operations in Montrose, Scotland where the drug substance, for Naratriptan will be manufactured in bulk and Glaxo Wellcome Operations in Dartford at which the drug substance will be milled and finally, Glaxo Wellcome Operations in Ware at which the tablets will be made. Attachments 1, 2, and 3 contain the certifications for Montrose, Dartford and Ware respectively.

Drug Product Packaging

No emission requirements apply to the packaging process at the Zebulon facility.

A Material Safety Data Sheet (MSDS) for Naratriptan is included under the research name of GR85548A as Attachment 4.

6.d. Effect Of Approval On Compliance With Emission Requirements

Drug Substance and Product Manufacturing

As provided for in Section VI of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995), certifications are provided for Glaxo Wellcome Operations in Montrose, Scotland where the drug substance, for Naratriptan will be manufactured in bulk and Glaxo Wellcome Operations in Dartford at which the drug substance will be milled and finally, Glaxo Wellcome Operations in Ware at which the tablets will be made. Attachments 1, 2, and 3 contain the certifications for Montrose, Dartford and Ware respectively.

Drug Product Packaging

There are no regulatory requirements for expected emissions from the packaging process and therefore no expected impact on compliance.

6.e. Expected Introduction Concentrations

6.e.i. Expected Introduction Concentrations From Use

Administered drug product will enter the environment primarily through wastewater treatment facilities. The expected introduction concentration (EIC) for the aquatic compartment from the use of all Naratriptan products and indications has been calculated to be less than 1ppb (CONFIDENTIAL Attachment A).

6.e.ii. Introductions from Product Disposal

It is estimated that there will be no emissions to the environment from product disposal. All product in the United States that is returned is completely destroyed by high-temperature incineration at the Greenville facility and under the permits discussed in Section 4.e..

7. FATE OF SUBSTANCES IN THE ENVIRONMENT

As discussed in Section 6.e.i the EIC for the aquatic compartment is expected to be less than 1 ppb. As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

9. USE OF RESOURCES AND ENERGY

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

10. MITIGATION MEASURES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

11. ALTERNATIVES TO THE PROPOSED ACTION

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

12. LIST OF PREPARERS

This EA was prepared by:

HORACE G. ROZIER Jr.

- Certified Hazardous Materials Manager
- Environmental Engineer, Glaxo Wellcome Inc. 1993 - present
- Chemist, Ecoflo Inc. 1989-1993
- Chemist, Compuchem Environmental Corporation 1989
- Bachelor of Science in Biochemistry & Microbiology
North Carolina State University , 1989

13. CERTIFICATION

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

The undersigned official certifies that the EA summary document pages 1-10 and Attachments 1-4 contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR 1506.6.



Thomas F. Cecich

MARCH 10, 1997

Date

Vice President, Environmental Safety
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

14. REFERENCES

Center for Drug Evaluation and Research, "Guidance For Industry For the Submission Of An Environmental Assessment In Human Drug Applications And Supplements," Federal Register, November 1995

Council On Environmental Quality, " Regulations On Implementing National Environmental Policy Act Procedures," Federal Register, Vol. 43, November 29, 1978, p. 55990.

Pharmaceutical Manufacturers Association, "Interim Guidance To The Pharmaceutical Industry For Environmental Assessment Compliance Requirements For The FDA v7," Seminar on Environmental Assessments, Rockville, Md., July 29-30, 1991.

U.S. FDA, "Environmental Assessment Technical Assistance Handbook," U.S. FDA, March 1987

U.S. FDA, "National Environmental Policy Act; Policies and Procedures; Final Rule," Federal Register, Vol. 50, April 26, 1985

15. APPENDIXES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

ATTACHMENTS

Attachment 1 Foreign Manufacturing Compliance Certification - Montrose

The Glaxo Wellcome manufacturing facility in Montrose, Scotland certifies that the facility is in compliance with or on an enforceable schedule to be in compliance with all local and national environmental laws and regulations including emission requirements set forth in permits, consent decrees and administrative orders, applicable to the production of Naratriptan Tablets. Any increase in production at the facility needed to support the requested approval is not expected to affect compliance with current emission requirements or compliance with environmental laws and regulations.



Steve Davis

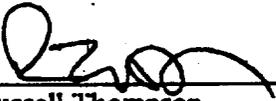
1/10/96.

Date

Safety, Health and Environmental Manager
10 Cobden Street
Montrose
Angus DD10 SE13
Scotland, United Kingdom

Attachment 2 Foreign Manufacturing Compliance Certification - Dartford

The Glaxo Wellcome manufacturing facility in Dartford, United Kingdom certifies that the facility is in compliance with or on an enforceable schedule to be in compliance with all local and national environmental laws and regulations including emission requirements set forth in permits, consent decrees and administrative orders, applicable to the production of Naratriptan Tablets. Any increase in production at the facility needed to support the requested approval is not expected to affect compliance with current emission requirements or compliance with environmental laws and regulations.



Russell Thompson

1 October 1996
Date

Environment Protection Manager
Glaxo Wellcome Operations
Temple Hill
Dartford
Kent
DA1 5AH
England

Attachment 3 Foreign Manufacturing Compliance Certification - Ware

The Glaxo Wellcome manufacturing facility in Ware, England certifies that the facility is in compliance with or on an enforceable schedule to be in compliance with all local and national environmental laws and regulations including emission requirements set forth in permits, consent decrees and administrative orders, applicable to the production of Naratriptan Tablets. Any increase in production at the facility needed to support the requested approval is not expected to affect compliance with current emission requirements or compliance with environmental laws and regulations.

G Ogden



Date

30/10/96

Safety and Environment Manager
Glaxo Wellcome Operations
Priory Street
Ware, Hertfordshire
SG12 0DJ England

Attachment 4

MSDS for Naratriptan (GR85548A)

MATERIAL SAFETY DATA SHEET

GR85548A
RESEARCH COMPOUND

Glaxo Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Emergency Contact:
Environmental Safety
(919) 248-2100
(919) 248-2700 (24 hour contact)

Revision Date: 04/30/97

SECTION I -- General Information

Chemical Name: N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide hydrochloride

CAS No.: 121679-13-8

Chemical Family: Piperidine derivative

Agent Name/Synonyms: GR85548A; GG548; naratriptan HCl

Molecular Weight: 361.9

Molecular Formula: $C_{17}H_{25}N_3O_2S.HCl$

SECTION II -- Hazardous Ingredients / Identity Information

Hazardous Components	%	Glaxo Limits	OSHA Limits	ACGIH Limits	Other limits (source)
GR85548A	100.00	Not established ug/m3 (OEL)	Not established (PEL)	Not established (TLV)	Not established (NIOSH Limit)

SECTION III -- Physical / Chemical Characteristics

Boiling Point: Not Applicable

Vapor Pressure (mm Hg): Not Applicable

Vapor Density (air = 1): Not Applicable

Evaporation Rate: Not Applicable

Solubility: Soluble in water.

Appearance & Odor: White to pale yellow solid; Odorless

Disclaimer: The information herein contained is believed to be accurate based on information currently available. Glaxo Inc. assumes no liability resulting from use or reliance therein. Any determination as to the suitability of the product for any particular purpose, its safe use or disposal shall be the responsibility of the user. Glaxo Inc. makes NO EXPRESS AND NO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR ANY PARTICULAR PURPOSE OR OTHERWISE WITH REGARD TO SUCH PRODUCT.

SECTION IV -- Fire & Explosion Hazard Data

Flash Point (test method): Not Applicable

LEL: Unknown

UEL: Unknown

Extinguishing Media: Water Spray, Multi-purpose Dry Chemical.

Special Fire Fighting Procedures: Wear full protective clothing and use self-contained breathing apparatus (SCBA).

Unusual Fire & Explosion Hazards: As with any organic dust, there is potential for explosion when suspended in air in high concentrations.

SECTION V -- Reactivity Data

Stability: Stable.

Hazardous Polymerization: NA

Incompatibility (materials to avoid): No known incompatibilities.

SECTION VI -- Health Hazard Data

Glaxo Occupational Exposure Limits

The provisional Glaxo safe working level is an eight-hour time-weighted average (TWA) of 0.05 mg/m³.

Pharmacologic Activity

GR85548A is the hydrochloride of GR85548X, a potent 5-hydroxytryptamine-like receptor agonist. It is intended for medical use in the treatment of migraine and cluster headaches by acting on blood vessels of the brain. However, it is not chemically or pharmacologically related to the narcotic-, analgesic-, or ergotamine-containing drugs also used to treat these conditions.

Occupational Health Hazards

Skin: This compound is not irritating or allergenic to normal skin, but may irritate damaged skin. GR85548A may be absorbed through the skin.

Inhalation: GR85548A is a pharmacologically active compound which may be absorbed by inhalation.

Eye Contact: This chemical is a mild eye irritant.

SECTION VI -- Health Hazard Data (Continued)

There is very limited experience with GR85548A in the occupational setting. Therefore, it should be handled in a manner which prevents exposure by any route. Protect against skin contact. Avoid generating or breathing dusts, aerosols, or vapors containing this compound.

Medical Conditions Aggravated by Exposure

Persons with uncontrolled high blood pressure or coronary heart disease may be at increased risk from exposure.

Toxicity Data

Acute Toxicity:

GR85548A has been administered to humans as single intravenous or subcutaneous doses. Short-lived side effects similar to those seen with other compounds of this class, e.g., sumatriptan succinate, have occurred. These include warmth, heaviness, pressure or other sensations (predominantly in the head and neck), tingling in the extremities and sweating. Chest symptoms (pressure, pain or tightness), and elevation of blood pressure have been reported after treatment with similar compounds. Rats tolerate single high doses given by mouth well, but large intravenous doses are immediately lethal. Dogs show mild symptoms of toxicity (dilation of the pupil of the eye, increased heart rate) with moderate intravenous doses.

Chronic Toxicity:

Testing to determine whether this compound causes cancer, birth defects or other reproductive health effects has not been performed. Rats were unaffected by very high oral doses given daily for one month with the exception of changes in the testes seen only with the most extreme dose.

Note: Some studies with sumatriptan succinate, a chemical similar to GR85548A, have shown toxic effects, including malformations, to the unborn offspring of rabbits treated with intravenous doses high enough to cause maternal toxicity. Studies with single compounds from a group of related chemicals do not always predict the potential health effects of untested members of the group. It is not known whether these effects or others will be seen with GR85548A. Therefore, it should be handled in a manner which prevents exposure by any route.

Genotoxicity:

This compound is not mutagenic (DNA-damaging) in standard tests with bacteria. Studies have shown that GR85548A may be converted to a mutagenic product if mixed with chemicals found in some foods (nitrites).

Emergency and First Aid Procedures

Eyes:

Flush thoroughly with large amounts of water. Obtain medical attention.

Skin:

Wash all affected areas thoroughly after removing contaminated clothing. Obtain medical attention.

SECTION VI -- Health Hazard Data (Continued)

Inhalation: Remove to fresh air. If breathing is difficult or ceases, give oxygen or cardiopulmonary resuscitation. Obtain medical attention.

Ingestion: Rinse mouth with water. Obtain medical attention.

SECTION VII -- Precautions for Safe Handling and Use

Spill and Leak Procedures: Full protective equipment including respirator, gloves, eye protection, and protective clothing should be worn where there is potential for skin exposure or risk of dust inhalation. Collect spillage by carefully sweeping or by vacuuming with HEPA filtered vacuum and place in labeled, sealed container for reuse or disposal. Wash area with suitable cleaning solvent after vacuuming.

Waste Disposal Methods: Incinerate at an approved facility in accordance with federal, state, and local regulations.

Handling and Storage Precautions: Small quantities in solution may be handled on open benches. A glove-gox should be used for dispensing and weighing this compound as a solid. Avoid exposure by any route. Use storage and handling practices that will avoid creation of dust, aerosols or vapors containing this chemical. Store between 2 and 30 degrees C in clearly-labeled, air-tight containers protected from light.

SECTION VIII -- Control Measures

Ventilation: Provide local exhaust ventilation at the source of dust generation.

Respiratory Protection: Respiratory protective equipment may be necessary to provide additional protection. The respirator should be certified by NIOSH (National Institute for Occupational Safety and Health) for dusts with a permissible exposure limit of < 0.05 mg/m³. Air-purifying or supplied-air respirators with a hood or with a full facepiece and a separate hood covering should be used.

Eye Protection: In areas of high dust concentration, workers should wear full skin coverings that will provide adequate eye protection from dust.

Clothing: In areas of low dust concentration, a protective outer garment may provide adequate worker protection. In dusty areas, full body protection should be used. All skin contact should be avoided.

Gloves: Protective gloves should be worn at all times to avoid skin contact.

Work Practices: Special care should be taken to ensure that contaminated clothing and equipment are properly cleaned after use.

Hygienic Practices: Workers exposed to dust should change clothes and shower at the end of the work assignment.

*** End of MSDS ***