CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020745

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

Jo Ilkendt

MAR 16 2007

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

ZANTAC® 75
(RANITIDINE HYDROCHLORIDE)
EFFERdose®
TABLETS
75 mg

NDA 20-745

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF GASTROINTESTINAL AND
COAGULATION DRUG PRODUCTS
HFD-180

FINDING OF NO SIGNIFICANT IMPACT
NDA 20-745
ZANTAC® 75
(raniditine hydrochloride)
EFFERdose®
Tablets

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 Zantac® 75 EFFERdose® Tablets, Glaxo Wellcome Incorporated has prepared an environmental assessment (attached) in accordance with 21 CFR 25.31(a), which evaluates the potential environmental impact of the manufacture, use and disposal of the product.

Ranitidine Hydrochloride is a synthetic drug which is used in the treatment of episodic heartburn. EFFERdose® is an alternate form of Zantac® for patients who have difficulty swallowing, or prefer a liquid dose. The finished drug product will be manufactured by Glaxo Wellcome Manufacturing, Evreux Cedex 9,27000 Evreux, France.

Ranitidine Hydrochloride may enter the environment from excretion by patients, from disposal of pharmaceutical waste and from emissions from manufacturing sites.

Based on the toxicity information provided, adverse environmental effects are not anticipated at the expected introduction concentration of the drug into the environment.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partially used product and packaging. Returned and expired drug product will be disposed of at a licensed incineration facility. From home use, empty or partially

landfill facility. 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.

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/S/

Feb 18, 1997
DATE

PREPARED BY:
Joseph Sieczkowski, Ph.D.
Review Chemist
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of New Drug Chemistry II

/S/

5/7/97
DATE

DIVISION CONCURRENCE:
Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of New Drug Chemistry II

/S/

5/16/97
DATE

APPROVED:
Nancy B. Sager
Environmental Scientist, HFD-357
Center for Drug Evaluation and Research

ATTACHMENTS:
Environmental Assessment, Material Safety Data Sheet (Drug Substance).

FONSI for NDA 20-745

cc:
HFD-357/NSager
HFD-820/JGibbs
HFD-181/MFolkendt
HFD-180/Joseph Sieczkowski
HFD-180/EDuffy
dob/F/T 2-12-97/WP: c:\wpfiles\chem\N\20745701.1JS

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1. DATE

June 12, 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 Zantac® 75 EFFERdose® for the treatment of episodic heartburn as a product available over the counter. EFFERdose® will be packaged in aluminum foil strips. The recommended adult dosage is one 75 mg tablet twice daily. This EA is submitted pursuant to 21 CFR Part 25.31a(a).

4.b. Need for the Action

Zantac® is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. It inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin. EFFERdose® is an alternate form of Zantac® for patients who have difficulty swallowing, or who prefer a liquid product.

4.c. Locations where Products will be Produced

The drug substance, ranitidine hydrochloride, will be manufactured in bulk at Glaxo Wellcome Operations' in Montrose, Scotland and the Glaxo Wellcome Manufacturing Pte Ltd facility in Jurong Singapore.

The drug product Zantac® 75 EFFERdose® will be manufactured and packaged by Glaxo Wellcome Manufacturing in Evreux, France.

The address of the Glaxo Wellcome Operations' Montrose facility is:

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

Glaxo Wellcome Operations' 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 Glaxo Wellcome Manufacturing Pte Ltd manufacturing facility in Jurong Singapore is as follows:

Glaxo Wellcome Manufacturing Pte Ltd
1 Pioneer Sector 1
Jurong, Singapore 628413

Jurong is an industrial new town and has been extensively developed and industrialized. The nearest residential area is approximately 5 km from the site. The facility is surrounded to the south by open sea and west by the Straits of Johore. To the east is a harbor and to the north are commercial and industrial facilities. The local weather is typical of a tropical, maritime climate. The Jurong site manufacturing facilities cover 22.5 acres and contain manufacturing departments, offices, storage areas, laboratories, workshops, and a number of ancillary buildings

The address of Glaxo Wellcome Operations Annan facility is

Glaxo Wellcome Operations
Three Trees Road
Newbie, Annan
Dumfriesshire DG12 5QH
Scotland, United Kingdom

Glaxo Wellcome Operation's Annan facility is situated in a rural area of Dumfriesshire in the southwest of Scotland on the shores of the Solway Firth, about 3 miles from the market town of Annan. The factory occupies an area of approximately 29 acres and an additional 90 acres of land is owned by the company for possible future development. A portion of this unused land is leased for agricultural purposes. The factory contains manufacturing departments, offices, stores, laboratories and workshops. The company manufactures two categories of bulk pharmaceutical chemicals: one final stage and one intermediate bulk pharmaceutical chemical.

The address of Glaxo Wellcome Manufacturing Evreux is:

Glaxo Wellcome Manufacturing
23, Rue Lavoisier
Zone Industrielle No. 2
EVREUX CEDEX 9
27000 Evreux
France

Evreux is the capital of Eure in northwest France. It is located approximately 100 kilometers from Paris. The town (population around 51,000) covers an area of approximately 2471 hectares. The Glaxo Wellcome Manufacturing facility is located in an industrial zone which covers an area of 84 hectares in a rural setting which is partially surrounded by the Evreux Forest. The facility is located on 15 hectares of which 4.6 hectares are covered by 15 buildings.

4.d. Sites of Product Use

Zantac® 75 EFFERdose® will be dispensed over the counter in 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 648°C (1200°F) in the primary chamber to 1010°C (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** - ranitidine hydrochloride

ii. **Proprietary Name** - Zantac®

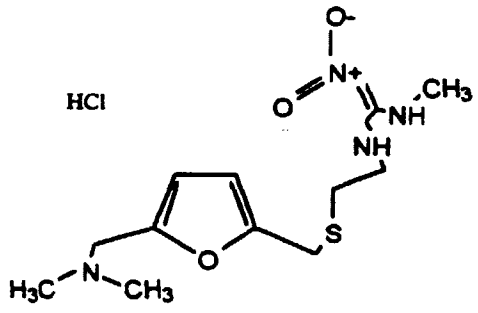
iii. **Chemical Name** - N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride

5.b. CAS Number - 066357-35-5

5.c. Molecular Formula - $C_{13}H_{22}N_4O_3S \cdot HCl$

5.d. Molecular Weight - 350.87

5.e. Structural Formula



5.f. Physical Description

Ranitidine hydrochloride is a white to pale yellow, granular substance.

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5.g. Additives

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

Aspartame	22389-47-0
Povidone 30 USP	9003-39-8

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5.h. Impurities

The specifications for ranitidine hydrochloride require that no single impurity will be

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

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6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.a. Substances Expected To Be Emitted

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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's facilities located in Montrose, Singapore, Annan, and Evreux

6.b. Controls Exercised

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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's facilities located in Montrose, Singapore, Annan, and Evreux

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

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's facilities located in Montrose, Singapore, Annan, and Evreux

A Material Safety Data Sheet (MSDS) for ranitidine hydrochloride is included as Attachment 5.

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

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's facilities located in Montrose, Singapore, Annan, and Evreux

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) from the use of all ranitidine hydrochloride products and indications including Zantac® 75 EFFERdose® is provide in CONFIDENTIAL

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 facilities and under the permits discussed in Section 4.e.

7. FATE OF SUBSTANCES IN THE ENVIRONMENT

The major route of drug substance emission into the environment is excretion following product use and subsequent release into wastewater collection and treatment systems. All returned and rejected drug product will be disposed of via high-temperature incineration. When administered to humans, the principal route of excretion of ranitidine hydrochloride is the urine. Available data indicate that the drug is, to a great extent, excreted unchanged. The three primary metabolites of ranitidine hydrochloride in humans are ranitidine-N-oxide, ranitidine-S-oxide, and N-desmethyl-ranitidine. These compounds have been measured in the urine at only 4%, 1%, and 1%, respectively, of the administered dose (Physicians' Desk Reference 1993). Furthermore, each of these metabolites are more polar than the parent compound.

Thus, ranitidine hydrochloride metabolites are not expected to be emitted in large amounts, relative to the amounts of ranitidine hydrochloride, as a result of usage by humans, and any metabolites that are excreted are not expected to be more environmentally persistent than ranitidine hydrochloride. Accordingly, these compounds are not considered significant for the purposes of this environmental assessment and will not be further evaluated. The fate and effects of chemical substances in the environment are predominately determined by their physical, chemical, and biological characteristics. To determine the environmental fate and effects of ranitidine hydrochloride, several laboratory studies were carried out in accordance with guidelines provided in the Food and Drug Administration (FDA) Environmental Assessment Technical Assistance Handbook. The results of these studies are summarized in Table 1. The complete environmental fate and effects study reports are provided in Appendix 10 of the EA for NDA 20-251 Zantac® EFFERdose™ Tablets and Granules.

As noted above, the major route of drug substance emission into the environment is via excretion in the urine and feces following product use and subsequent release into wastewater collection and treatment systems. Ranitidine hydrochloride was found to be hydrolytically stable over all pH ranges tested; thus, hydrolysis cannot be considered an important removal process. Based on consideration of the Pharmaceutical Manufacturers Association/Food and Drug Administration (PMA/FDA) Environmental Assessment Technical Test Matrix, the results of the minimum data base fate tests indicate that ranitidine hydrochloride will localize primarily into the aquatic environmental compartment:

- the water solubility of this substance is much greater than 10^{-5} Molar,
- the log octanol/water partition coefficient is much less than 2, and
- the vapor pressure is much less than 10^{-7} Torr.

Transport of ranitidine hydrochloride into the terrestrial and atmospheric compartments is expected to be negligible by comparison.

Aquatic Ecosystems

A major determinant of the fate of ranitidine hydrochloride in the aquatic compartment is its rate of degradation. Thus, a determination of its aerobic biodegradation in water was carried out in accordance with the FDA Environmental Assessment Technical Handbook, 3.11. The results of this test indicated to CO_2 occurred over the 28-day test period. Thus, ranitidine hydrochloride does not meet the current FDA criteria for ready biodegradability (i.e., half-life less than approximately 8 hours for aerobic biodegradation). According to the PMA/FDA Guidelines for preparing environmental assessments, the relatively low octanol/water partition coefficient, indicates that ranitidine hydrochloride is unlikely to bioaccumulate in the tissues of aquatic organisms. Since the fate studies show that the drug substance does not hydrolyze or degrade, it is assumed that the expected introduction concentration (EIC) is equal to the maximum expected environmental concentration (MEEC).

Table 1 Summary of Environmental Fate and Effects Studies Conducted on Ranitidine Hydrochloride

Study Name	Results			
hydrolysis rate	hydrolytically stable over all pH ranges.			
vapor pressure	1E-09 Torr at 25°C (by extrapolation)			
uv/visible spectra at pH 7	peak	molar absorption coefficient	wavelength	absorbance
	1	19557	227.2nm	1.114
	2	18504	313.2nm	1.054
octanol/water partition coefficient	Log10 K_{ow} at			
	pH5	pH7	pH9	
	-2.5	-1.1	0.14	
dissociation constant	pK_a = 8.29 at pH 10			
water solubility at 20.5C	pH 5	pH 7	pH9	
	1026 g/l	947 g/l	934 g/l	
soil sorption/desorption	soil type	pH	Ko_C	
	silty clay loam	5.0	31,000	
	sandy loam	5.8	1,400	
	sandy loam	7.0	320	
biodegradation in soil	3 to 10% mineralization to CO_2 in 67 days			
biodegradation in water	< 1% mineralization to CO_2 in 28 days			
* ASRIT	EC_{50} => 893 mg/l Ranitidine base (>1000 mg/l ranitidine HCL)			
acute toxicity to daphnids	EC_{50} = 650 mg/l Ranitidine base (730 mg/l ranitidine HCL)			

* Activated Sludge Respiration Inhibition Test (ASRIT) reflects microbial inhibition in wastewater treatment facilities.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

No published studies evaluating the potential environmental toxicity of ranitidine hydrochloride were identified. Therefore, two studies were carried out to evaluate the acute effects of ranitidine hydrochloride on potential environmental receptors: (1) the Activated Sludge Respiration Inhibition Test, and (2) a test of acute toxicity to *Daphnia magna*. The results of these studies are summarized in Table 1. These tests were determined to be most appropriate for evaluating the effects of ranitidine hydrochloride in the environment.

Emissions to the environment are expected to occur primarily following use of the drug product and would result in release to wastewater treatment plants and, ultimately, to surface water.

The Activated Sludge Respiration Inhibition Test determined the toxicity to activated sludge microorganisms, typical of those found in municipal sewage treatment facilities, by a respirometric method. The test was carried out according to Organization for Economic Cooperation and Development (OECD) Test Guideline 209 under conditions sufficient to satisfy the requirements of the FDA Good Laboratory Practice Regulations (21 CFR 58). Test concentrations were 10, 100, and 1,000 mg/L ranitidine hydrochloride (equivalent to 8.9, 89.3, and 892.9 mg/L ranitidine base). No inhibition of microbial respiration was observed up to and including the maximum concentration used, giving a 3-hour median effect concentration (EC_{50}) and a no observed effect concentration of >1,000 mg/L ranitidine hydrochloride (equivalent to >893 mg/L ranitidine base). The complete environmental fate and effects study reports are provided in Appendix 10 of the EA for NDA 20-251 Zantac® EFFERdose® Tablets and Granules.

The acute toxicity to *Daphnia magna* was evaluated according to procedures identified in FDA Technical Assistance Document 4.08. The test determines a median effect concentration (EC_{50}), defined as the concentration resulting in 50% immobilization of the *Daphnia* in the specified time period. The *Daphnia* acute aquatic toxicity study identified 24-hour and 48-hour EC_{50}s of >1800 mg/L and 730 mg/L ranitidine hydrochloride, respectively (equivalent to >1600 mg/L and 650 mg/L ranitidine base, respectively).

Evaluation of Environmental Effects

Small amounts of ranitidine hydrochloride may be excreted by individuals using Zantac® 75 EFFERdose® and ultimately may enter the aquatic environment through wastewater treatment plants. The results of the toxicity testing as compared with the maximum expected environmental concentration of the active moiety show that the release of ranitidine hydrochloride into the environmental should be considered nontoxic as per the Center for Drug Evaluation and Research, "Guidance For Industry For the Submission Of An Environmental Assessment In Human Drug Applications And Supplements", since the ratio of the EC_{50} divided by the maximum expected environmental concentration (MEEC) is

No adverse environmental effects are expected to occur as a result of emissions associated with Zantac® 75 EFFERdose® manufacturing processes. Emissions of all substances are within regulatory limits or are collected and disposed of using appropriate, approved procedures.

No adverse environmental effects are expected to occur as a result of emissions associated with disposal of returned or Zantac® 75 EFFERdose®. All returned drug products are incinerated at approved facilities capable of destroying the drug substance, excipients, and packaging materials.

9. USE OF RESOURCES AND ENERGY

The raw materials used in the production of ranitidine hydrochloride and Zantac® 75 EFFERdose®, including the substances used as excipients in the final dosage form, are readily available. The production of this drug product will not cause significant depletion of any natural resources, including energy, minerals/chemicals, and land.

A review of the manufacturing processes considered in this environmental assessment indicates that the energy resources required to produce and distribute Zantac® 75 EFFERdose® are in a range which is considered normal for production and distribution of a pharmaceutical product.

10. MITIGATION MEASURES

For all sites, it is projected that no additional structural controls will be needed in order to comply with applicable environmental regulations and permits. However, many non-structural environmental controls which are implemented at the facilities as standard procedures will have the effect of being mitigation measures for the proposed action. Furthermore, standard emergency response procedures will have the effect of being mitigation measures for the proposed action.

Spill Prevention Control and Countermeasures

All Glaxo Wellcome sites have emergency procedures designed to prevent or minimize the environmental effects of any potential release of hazardous materials from any of the production units. Summaries of site procedures are outlined in the respective manufacturing site environmental assessments.

Waste Minimization

Glaxo Wellcome facilities actively pursue opportunities to minimize waste generated at manufacturing facilities. of the original EA for Zantac® 75 EFFERdose™ Tablets and Granules, provide additional information on the specific initiatives undertaken to minimize waste at each facility.

Solid and Hazardous Waste Management Procedures

All waste disposal contractors are subjected to audits by Glaxo Wellcome or a nominated consultant to ensure that they comply, at a minimum, with the legal standards. These audits consist of site visits as well as full review of the contractors' policies and licenses.

Chemical Hygiene Procedures

Glaxo Wellcome uses engineering controls to reduce or eliminate chemical exposure in the workplace wherever such controls are technically and economically feasible. When engineering controls prove to be not feasible or provide insufficient protection, the use of personal protective equipment is required. Prior to the start up of new equipment and/or processes, acceptance tests are carried out on the control measures installed to prevent employee exposure.

Prior to production involving a new drug substance which could potentially expose employees to a chemical which has no established exposure limit, a committee develops an internal corporate occupational exposure limit (OEL). The committee members include Medical, Safety and Industrial Hygiene professionals, as well as other individuals knowledgeable about the chemical in question and its effects.

Emission Controls

In general, areas where releases are likely to contain pollutants are vented to appropriate scrubbers. Scrubbers are monitored on a regular basis. filtration are used in appropriate manufacturing areas.

11. ALTERNATIVES TO THE PROPOSED ACTION

The only alternative action is no action. The alternative would deny an over the counter form of a safe and effective drug to some segments of the public that could benefit from its use. The alternative action is not justified because no adverse environmental effects have been identified in this environmental assessment and none are expected to be associated with the production, use, and disposal of this product.

12. LIST OF PREPARERS

This EA was prepared by:

HORACE G. ROZIER Jr.

- Environmental Engineer, Glaxo Wellcome Inc. 1993 - present
- Chemist, 1989-1993
- Chemist, 1989
- Bachelor of Science in Biochemistry & Microbiology
  North Carolina State University , 1989

13. CERTIFICATION

APPEARS THIS WAY ON ORIGINAL

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 1-13 & Attachments 1-5, 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 — 12/13/96

Thomas F. Cecich — Date

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

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ON ORIGINAL

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.

Glaxo Wellcome "NDA 20-251 Zantac® EFFERdose™ Tablets and Granules", November 2, 1993.

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.

Physicians' Desk Reference, 47th Edition. 1993. Medical Economics Data. Montvale, NJ.

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. ATTACHMENTS & APPENDIXES

Attachment 1 Foreign Manufacturing Compliance Certification - Montrose

The Glaxo Wellcome Operations 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 Zantac® 75 EFFERdose®. 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.

28/5/96.

Steve Davis — Date

Safety, Health and Environmental Manager
Glaxo Wellcome Operations
Cobden Street
Montrose
Angus DD10 8EA
Scotland, United Kingdom

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ON ORIGINAL

Attachment 2 Foreign Manufacturing Compliance Certification - Jurong

The Glaxo Wellcome manufacturing facility in Jurong, Singapore 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 Zantac® 75 EFFERdose®. 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.

Alan Loh

5-6-96
Date

Director of Safety and Environment
Glaxo Wellcome Pharmaceutical Pte Ltd
1 Pioneer Sector 1
Jurong Singapore 628413

APPEARS THIS WAY
ON ORIGINAL

Attachment 3 Foreign Manufacturing Compliance Certification - Annan

The Glaxo Wellcome Operation's facility in Annan 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 Zantac® 75 EFFERdose®. 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.

Pamela Bond — 11.6.96

Pamela Bond — Date

Glaxo Wellcome Operations
Three Trees Road
Newbie, Annan
Dumfriesshire DG12 5QH
Scotland, United Kingdom

APPEARS THIS WAY
ON ORIGINAL

Attachment 4 Foreign Manufacturing Compliance Certification - Everux

The Glaxo Wellcome Operation's facility in Everux 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 Zantac® 75 EFFERdose®. 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.

Luc - PARENT — 10 JUNE 96

Luc Parent — Date

Glaxo Wellcome Manufacturing
23, Rue Lavoisier
Zone Industrielle No. 2
EVREUX CEDEX 9
27000 Evreux
France

APPEARS THIS WAY
ON ORIGINAL

Attachment 5

Material Safety Data Sheet (ranitidine hydrochloride)

MATERIAL SAFETY DATA SHEET

Zantac(R) (ranitidine hydrochloride) EFFERdose(TM) Granules and Tablets

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: 12/19/94

SECTION I -- General Information

Generic Name: Ranitidine hydrochloride

Chemical Name: N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride

Chemical Family: Furan derivative histamine receptor antagonist

Finished Product Name: ZANTAC(R) EFFERdose(TM) GRANULES & TABLETS

Agent Name/Synonyms: Zantac(R) (ranitidine hydrochloride) EFFERdose(TM) Granules and Tablets

SECTION II -- Hazardous Ingredients / Identity Information

Hazardous Components/CAS#	%	Glaxo Limits	OSHA Limits	ACGIH Limits	Other limits (source)
Ranitidine hydrochloride 150 mg/ CAS# 66357-59-3		0.05 mg/m3 (pure substance) (STEL)	Not established (PEL)	Not established (TLV)	Not established (NIOSH Limit)

SECTION III -- Physical / Chemical Characteristics

Boiling Point: Not determined.

Vapor Pressure (mm Hg): Not determined.

Vapor Density (air = 1): Not determined.

Specific Gravity (H_2O = 1): Not determined.

Melting Point: Not determined.

Evaporation Rate: Not determined.

SECTION III -- Physical / Chemical Characteristics (Continued)

Solubility: Not determined for Zantac(R) EFFERdose(TM). Ranitidine hydrochloride, the active ingredient in Zantac(R), is very soluble in water, methanol and ethanol.

Appearance & Odor: Odorless, round, white to pale yellow tablets; Odorless, white to pale yellow loose granules.

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 formulated, Zantac Tablets should be dust free. However, breakage of tablets, especially in bulk operations, could contribute to dust formation. As with any organic dust, there is potential for explosio when high concentrations are suspended in air.

SECTION V -- Reactivity Data

Stability: Stable.

Hazardous Polymerization: Will Not Occur

Conditions to Avoid: Not determined.

Incompatibility (mat'ls to avoid): Not determined for Zantac(R) EFFERdose(TM), No known incompatibilities have been identified for ranitidine hydrochloride. the active ingredient in Zantac(R).

Hazardous Decomposition Products: Not determined for Zantac(R) EFFERdose(TM). Thermal decomposition products of ranitidine hydrochloride, the active ingredient in Zantac(R), may include toxic and/or corrosive vapors consisting of chlorides and oxides of nitrogen and sulfur.

SECTION VI -- Health Hazard Data

THE RISK OF HEALTH HAZARDS MAY BE REDUCED WHEN ZANTAC(R) EFFERdose(TM) GRANULES & TABLETS IS HANDLED IN A UNIT DOSAGE FORM.

SECTION VI -- Health Hazard Data (Continued)

Glaxo Occupational Exposure Limits

For ranitidine hydrochloride, the active ingredient in Zantac(R) EFFERdose Granules and Tablets, the Glaxo estimated safe working level is a 15-minute short term exposure limit (STEL) of 0.05 mg/m3.

Pharmacologic Activity

Ranitidine hydrochloride is a competitive, reversible inhibitor of the action of histamine at histamine H2-receptors, including those o cells of the digestive tract. Therapeutically, Zantac(R) EFFERdose Granules and Tablets are used to treat pathological gastric acid overproduction, gastrointestinal ulcers, gastroesophygeal reflux disease (backflow of stomach contents into the esophagus), erosive esophagitis (inflammation of the lining of the esophagus), and to provide maintenance therapy for these conditions.

Signs and Symptoms of Occupational Exposure

Acute Effects:

Overexposure to ranitidine hydrochloride in the occupational setting may result in the same adverse effects which have been observed when ranitidine is used medically.
Ranitidine hydrochloride may cause skin irritation, burning, itching, redness, or rash in sensitive individuals. Exposure to ranitidine dust may cause allergic reactions with symptoms ranging from skin rashes, hives, runny or stuffy nose, chest tightness, and difficulty breathing to anaphylaxis (a severe allergic reaction which may include shortness of breath, unconsciousness, convulsions, and shock).

Chronic Effects:

Headache, sometimes severe, may result from medicinal use of ranitidine hydrochloride. Rarely, malaise, dizziness, drowsiness or insomnia have been reported. Rare reports of erratic heartbeat (including increased or decreased heart rate and premature beats) exist. Ranitidine has been reported to cause constipation, diarrhea, nausea/vomiting and abdominal discomfort or pain. Some individuals using ranitidine have elevated blood levels of SGPT (an enzyme which when increased in blood may indicate liver damage). Rare cases of liver inflammation and liver damage (with or without jaundice) have occurred. Hypersensitivity reactions ranging from bronchospasm, rashes, and fever to rare cases of anaphylaxis (a severe allergic reaction which may include shortness of breath, unconsciousness, convulsions, and shock) have occurred in some individuals. Repeated exposure to ranitidine dust may cause skin rash, nasal runniness and congestion, and shortness of breath with wheezing.

Occupational Health Hazards

Skin:

Repeated skin contact can lead to sensitization, which may result in an allergic (red, itchy) skin rash.

SECTION VI -- Health Hazard Data (Continued)

Inhalation: Dust exposure may irritate mucous membranes. In unusual cases, prolonged exposure to ranitidine hydrochloride dust has been associated with shortness of breath and wheezing.

Eye Contact: Avoid contact with the eyes.

Ingestion: Ingestion in sufficient dose could result in the same adverse effects that have been observed with ranitidine used clinically (see Section VI - "Signs and Symptoms of Occupational Exposure"). EFFERdose(TM) tablets and granules will release CO2 upon ingestion, possibly causing a feeling of fullness or bloating.

Medical Conditions Aggravated by Exposure

Individuals known to be hypersensitive to ranitidine hydrochloride should not be exposed.

Toxicity Data

Ranitidine does not cause cancer, mutation (change in the genetic material), birth defects or other reproductive health effects in standard tests. There are, however, no adequate and well-controlled studies of the effects of ranitidine in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed. For recommended dosage and administration, Zantac(R) EFFERdose Granules and Tablets are classified as "Pregnancy Category B". Ranitidine is excreted in human milk. Caution should be exercised when Zantac(R) is administered to a nursing mother. In the occupational setting, exposure to Zantac(R) EFFERdose(TM) Granules and Tablets should be medically evaluated during pregnancy or nursing.

Emergency and First Aid Procedures

Eyes: Flush with large amounts of cool water for at least 15 minutes. Obtain medical attention.

Skin: After removing contaminated clothing, wash affected areas with soap and water. Obtain medical attention if contamination is significant and/or skin reaction is evident.

Inhalation: If not breathing, give artificial respiration or CPR. If breathing is difficult, give oxygen. Obtain medical attention.

Ingestion: If awake and able to swallow, rinse mouth with water. Never give anything by mouth if unconscious or having convulsions. Obtain medical attention.

SECTION VII -- Precautions for Safe Handling and Use

Spill and Leak Procedures: Protective equipment may be necessary for spills. (See Section VIII - "Control Measures" for guidance.)
For small quantities associated with normal therapeutic use, collect spillage and transfer to a closed waste container for disposal. For large or bulk quantities, collect spillage by carefully sweeping or wiping and place in a labelled, sealed container for disposal. Wash spill area (floor and other contact surfaces) thoroughly with water.

Waste Disposal Methods: Unused product should be disposed of at an approved facility in accordance with federal, state and local regulations.

Handling and Storage Precautions: Store between 36 and 86 degrees F in a dry place. Protect from excessive moisture and light. Replace cap securely.

SECTION VIII -- Control Measures

Ventilation: In areas of high dust concentration, provide good general exhaust ventilation.

Respiratory Protection: Respiratory protective equipment should be worn when workers are exposed to high dust levels. Recommendations for respirator selection issued by the National Institute for Occupational Safety and Health (NIOSH), the American National Standard Practices for Respiratory Protection (ANSI Z88.2) and the respirator equipment manufacturer should be followed.

Eye Protection: Not required for recommended dosage and administration. In areas of high dust concentration, workers should wear adequate eye protection to prevent eye contact.

Clothing: Adequate protective clothing should be worn to prevent occupational skin contact.

Gloves: When routine handling or spill cleanup may result in skin contact, impermeable (e.g., latex) gloves should be worn.

Work Practices: Special care should be taken to ensure that contaminated clothing, equipment, and work surfaces are properly cleaned or disposed of after use. A suitable cleaning solvent, such as soap and water, should be used, unless other standard operating procedures supercede these recommendations.

Hygienic Practices: Wash hands and other areas of skin contact thoroughly after handling this material. Contaminated clothing should be cleaned or disposed of.

SECTION IX -- Transportation

SECTION IX -- Transportation (Continued)

Surface

DOT Proper Shipping Name: Nonhazardous for transportation purposes.

Air

IATA Proper Shipping Name: Nonhazardous for transportation purposes.

***** End of MSDS *****

APPEARS THIS WAY
ON ORIGINAL