CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20768

CHEMISTRY REVIEW(S)

MAY 1 4 '97

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-768

CHEMISTRY REVIEW: # 1 **DATE REVIEWED:** 22-APR-97

Submission Type	Document Date	CDER Date	Assigned Date
Original	26-NOV-96	26-NOV-96	07-DEC-96
Amendment	28-FEB-97	04-MAR-97	06-MAR-97

NAME AND ADDRESS OF APPLICANT: Zeneca Pharmaceuticals, as US agent for IPR Pharmaceuticals, Inc.
1800 Concord Pike, P. O. Box 15437
Wilmington, DE 19850-5437

DRUG PRODUCT NAME:

Proprietary:	**ZOMIG™**
Nonproprietary/Established/USAN:	zolmitriptan
Code Name/#:	311C90
Chem. Type/Ther. Class:	**1 S**

DESI / PATENT STATUS: US Patent No. 5,466,699, expiration date November 14, 2012 covers composition, formulation and use of zolmitriptan tablets.

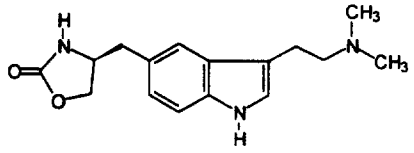
PHARMACOLOGICAL CATEGORY / INDICATION:	Migraine
DOSAGE FORM:	Tablets
STRENGTHS:	2.5 mg and 5.0 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	**XX Rx ___ OTC**

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

(S)-4-{[3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]methyl}-oxazolidinone

CAS No. 139264-17-8

$C_{16}H_{21}N_3O_2$ Mol. Wt. 287.36



SUPPORTING DOCUMENTS: N/A

RELATED DOCUMENTS (if applicable): IND for zolmitriptan

CONSULTS: Environmental Assessment, on consult to HFD-357, not completed.

REMARKS / COMMENTS:

Zolmitriptan (311C90) was originally developed by Glaxo Wellcome and sold to Zeneca to satisfy FTC requirements. Zeneca is currently obtaining drug substance from GW but will manufacture all drug product themselves. The drug substance manufacturing information is insufficient and the proposed regulatory controls for drug substance and drug product are not adequate. Inspections have not been completed and analytical method validation will not be initiated until deficiencies in the proposed methods are corrected.

CONCLUSIONS AND RECOMMENDATIONS:

NDA is NOT APPROVABLE for chemistry at this time.

cc: Orig. NDA 20-768
HFD-120/Division File

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-768

CHEMISTRY REVIEW: # 2 **DATE REVIEWED:** 17-OCT-97

Submission Type	Document Date	CDER Date	Assigned Date
N(BC) (Env. Ass.)	07-MAR-97	11-MAR-97	11-MAR-97
N(BC) (Env. Ass.)	19-MAY-97	22-MAY-97	22-MAY-97
N(BC) (Stability update)	21-MAY-97	22-MAY-97	22-MAY-97
N(BC) (Response to IR letter)	25-AUG-97	25-AUG-97	25-AUG-97

NAME AND ADDRESS OF APPLICANT: Zeneca Pharmaceuticals, as US agent for IPR Pharmaceuticals, Inc.
1800 Concord Pike, P. O. Box 15437
Wilmington, DE 19850-5437

DRUG PRODUCT NAME:
Proprietary: ZOMIG™ OCT 22 1997
Nonproprietary/Established/USAN: zolmitriptan
Code Name/#: 311C90
Chem. Type/Ther. Class: 1 S

DESI / PATENT STATUS: US Patent No. 5,466,699, expiration date November 14, 2012 covers composition, formulation and use of zolmitriptan tablets.

PHARMACOLOGICAL CATEGORY / INDICATION: Migraine
DOSAGE FORM: Tablets
STRENGTHS: 2.5 mg and 5.0 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

(S)-4-{[3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]methyl}-oxazolidinone

CAS No. 139264-17-8

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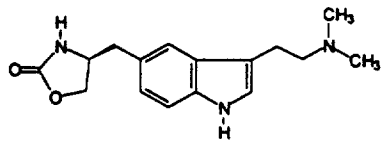

SUPPORTING DOCUMENTS: N/A

RELATED DOCUMENTS (if applicable): IND for zolmitriptan

CONSULTS: Environmental Assessment, consulted to HFD-357 by Project Manager, completed.
Trademark, Zomig®, is acceptable to Nomenclature Committee

REMARKS / COMMENTS:

Zolmitriptan (311C90) was originally developed by Burroughs Wellcome and sold to Zeneca to satisfy FTC divestiture requirements for the Glaxo - Burroughs Wellcome merger. Glaxo Wellcome (GW) is still the drug substance manufacturer. The 25-AUG-97 amendment provides responses to our 16-MAY-97 information request letter. Questions about the drug substance manufacturing process have been adequately answered but the proposed regulatory controls for drug substance and drug product are still not adequate

CONCLUSIONS AND RECOMMENDATIONS:

NDA is approvable for Chemistry provided that sponsor adequately addresses all deficiencies listed.

cc: Orig. NDA 20-768
HFD-120/Division File
HFD-120/MHeimann/17-OCT-97

Martha R Heimann 10/17/97

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-768

CHEMISTRY REVIEW: # 3 **DATE REVIEWED:** 06-NOV-97

Submission Type	Document Date	CDER Date	Assigned Date
N(BZ)	21-OCT-97	21-OCT-97	21-OCT-97
N(BL)	29-OCT-97	03-NOV-97	–

NAME AND ADDRESS OF APPLICANT: Zeneca Pharmaceuticals, as US agent for IPR Pharmaceuticals, Inc.
1800 Concord Pike, P. O. Box 15437
Wilmington, DE 19850-5437

DRUG PRODUCT NAME:

Proprietary:	**ZOMIG™**
Nonproprietary/Established/USAN:	zolmitriptan (officially adopted 1997)
Code Name/#:	311C90
Chem. Type/Ther. Class:	**1 S**

DESI / PATENT STATUS: US Patent No. 5,466,699, expiration date November 14, 2012 covers composition, formulation and use of zolmitriptan tablets.

PHARMACOLOGICAL CATEGORY / INDICATION:	Migraine
DOSAGE FORM:	Tablets
STRENGTHS:	2.5 mg and 5.0 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	XX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

(S)-4-{[3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]methyl}-oxazolidinone

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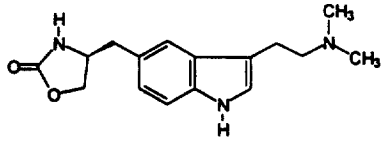


SUPPORTING DOCUMENTS: N/A

RELATED DOCUMENTS (if applicable): IND for zolmitriptan

CONSULTS: Environmental Assessment, consulted to HFD-357 by Project Manager, completed.
Trademark, Zomig®, is acceptable to Nomenclature Committee

REMARKS / COMMENTS:

The 21-OCT-97 and 29-OCT-97 submissions address the remaining deficiencies from review #2 and confirm Zeneca's agreement to several changes negotiated in telecons. [See record of telecons attached to review #2.] The revised drug substance/product specifications are summarized on p. 2 and include changes in the dissolution specification and method requested by the Biopharmaceutics reviewer. A 24 month expiration dating period for the drug product was accepted by the sponsor. The firm has committed to improve the precision and accuracy of the CE method used for determination of three drug substance impurities, 1765W92, 420C90 and 276C91. By agreement with the Division, a modified CE method will be submitted as a 'Changes Being Effected' supplement. [Target date is end of February 1998.] NDA Methods Validation will be initiated when the revised CE method is received.

CONCLUSIONS AND RECOMMENDATIONS:

Recommend that NDA be approved. Action letter should contain standard paragraph about cooperation in methods validation.

cc: Orig. NDA 20-768
HFD-120/Division File
HFD-120/MHeimann/06-NOV-97

Martha Rheimann

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20768

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

ZOMIG™
(ZOLMITRIPTAN)
Tablet
NDA 20-768

IPR PHARMACEUTICALS

U. S. FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION of NEUROPHARMACOLOGICAL DRUG PRODUCTS
(HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-768

ZOMIG™

(ZOLMITRIPTAN)

TABLET

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 it 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 Zomig™, IPR Pharmaceuticals has prepared an environmental assessment (attached) in accordance with *21 CFR 25.31a(a)*, which evaluates the potential environmental impact of the manufacture, use and disposal of the product. The maximum expected environmental concentration is at a level that normally relieves the applicant from completing format items 7, 8, 9, 10, 11, and 15 in accordance with the Tier 0 approach specified in the *Guidance for Industry for the submission of an Environmental Assessment in Human Drug Applications and Supplements.*

Zolmitriptan is a chemically synthesized drug which is administered as a tablet in the acute treatment of migraine attacks with or without aura. The drug substance will be manufactured by Glaxo-Wellcome Operations, Dartford, Kent and the drug product will be produced by IPR Pharmaceuticals, San Juan, Puerto Rico. The finished drug product will be used by patients in their homes.

Zomig drug substance may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

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 product will be disposed of at a licensed high temperature incineration facility.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The 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.

Carl J. Berninger

July 16, 1997
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

Nancy B. Sager

7/16/97
Date

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

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

ENVIRONMENTAL ASSESSMENT FOR ZOLMITRIPTAN

NDA 20-768

(UPDATE MAY 1997)

CONTENTS

ZOLMITRIPTAN ENVIRONMENTAL ASSESSMENT

SECTION 1. DATE:

February 1997

SECTION 2. APPLICANT

IPR Pharmaceuticals
Sabana Gardens
PO Box 1967
Main Street Carolina
San Juan
Puerto Rico 00628

ZENECA Pharmaceuticals a business unit of ZENECA Inc. is the authorised US agent for IPR Pharmaceuticals for the subject NDA

SECTION 3. ADDRESSES

Administrative Headquarters.

IPR Pharmaceuticals
Sabana Gardens
PO Box 1967
Main Street Carolina
San Juan
Puerto Rico 00628

Site for Manufacture of Active Agent

Glaxo Wellcome Operations
Temple Hill
Dartford
Kent DA1 5AH

Site for Manufacture of the Drug Product

IPR Pharmaceuticals
Sabana Gardens
PO Box 1967
Main Street Carolina
San Juan
Puerto Rico 00628

US Distribution Centre

ZENECA Pharmaceuticals
587 Old Baltimore Pike
Newark, Delaware 19702

SECTION 4. DESCRIPTION OF THE PROPOSED ACTION

4.1 Describe the requested action

IPR Pharmaceuticals is filing a new drug application for approval to manufacture and formulate, package and distribute zolmitriptan.

The US agent is: ZENECA Pharmaceuticals
1800 Concord Pike
Wilmington
Delaware
19850-5437

The NDA number is 20-768

Zolmitriptan is formulated as tablets containing 2.5 and 5.0 mg of the active drug substance which is also known as 311C90

4.2 Describe the need for the proposed action

Zolmitriptan is a new drug for the acute treatment of migraine attacks with or without aura.

4.3 Locations where the products are to be :-

4.3.1 Produced

The active material will be produced at the Glaxo-Wellcome manufacturing site at Dartford in the UK

The address of the facility is:-

Glaxo-Wellcome Operations
Temple Hill
Dartford
Kent DA1 5AH

4.3.2 Formulated and Packed

The active drug substance will be formulated and packed at the IPR facility in Puerto Rico.

The address of the facility is:-

IPR Pharmaceuticals
Sabana Gardens
PO Box 1967
Main Street Carolina
San Juan
Puerto Rico 00628

4.3.3 Distribution Centre for the USA

Distribution for the USA will be undertaken from the ZENECA Pharmaceutical Site in Delaware.

The address of the facility is:-

ZENECA Pharmaceuticals
587 Old Baltimore Pike
Newark, Delaware 19702

4.3.4 Used

Zolmitriptan is indicated as a new drug for the acute treatment of migraine attacks with or without aura. The product will be used by individuals throughout the USA.

4.3.5 Disposed

The product is used for the home treatment of patients with migraine. It is administered in tablet form. The packaging would be disposed of by the normal methods used for disposing of the packaging of medicinal products.

Any rejected, returned or time expired product will be disposed of by high temperature incineration in facilities approved by the local authorities having jurisdiction in the area in which disposal is taking place.

4.4 Types of location in which the manufacturing sites detailed in 4.3.1, 4.3.2 & 4.3.3 above are situated.

4.4.1 Site for Manufacture of Active Material

The Dartford Site is located on the banks of the River Darrent and Dartford Creek in an industrial area adjacent to the town of Dartford, Kent in the South East of England. Dartford is approximately 20 miles East from London, in the Thames Estuary region and has a population of around 82,000.

The land immediately adjacent to the production facility comprises residential property to the East and South with a mixture of industry and housing to the West. North of the Site are the North Kent Marshes which extend for a few miles to the River Thames estuary. Industry in the area has changed significantly in recent times, with the heavy engineering and paper making industries giving way to light industry, commerce and distribution companies.

Dartford town is surrounded by an area of Green Belt. There are a number of listed buildings in the area. However the area contains no endangered species as defined by European Commission Regulation No 3626/82.

The climate is temperate with average monthly temperatures ranging from 1.4-6.4^{0}C in January to 13-21.1^{0}C in July. The average wind speed is 11.6 knots and the mean rainfall is 525 mm per year.

The site has a thin layer of brickearth overlaying a chalk layer which is about 200 meters thick.

The chalk strata contains an aquifer which is abstracted to supply water for industrial use. The Glaxo-Wellcome site currently has four operational boreholes supplying ground water for cooling purposes.

The River Darrent flows into the River Thames. The tidal limit of the Darrent is controlled by a weir installed at the Glaxo-Wellcome Site. Downstream of this weir the Darrent is known as Dartford Creek.

In addition a network of drainage dikes on the North Site marshes direct a flow of water directly into the River Thames.

The pharmaceutical manufacturing and support facilities are enclosed in a secure area of 71 acres. There are in addition 64 acres which have not been developed.

4.4.2 Sites of Formulation and Packing Facilities

4.4.2.1 IPR, Carolina

The site at Carolina is located in an area designated as an industrial zone. It is bounded by other industrial property.

The site has been developed to provide facilities for the formulation and packing of pharmaceutical products. The buildings are of modern design and construction.

Waste water is transferred to PRASA (Puerto Rico Aqueduct and Sewer Authority) sewer system and treated at the Carolina Regional Wastewater Treatment Plant. The discharges are covered by a local permit.

4.4.2.2 Glaxo-Wellcome, Dartford

Reference is made to the February 28, 1997 submission to the ZOMIG NDA 20-768 in which Zeneca Pharmaceuticals notified the Agency, that pursuant to 21 CFR 314.65, the Glaxo Wellcome facilities in Dartford, United Kingdom has been withdrawn from the subject NDA as a commercial drug product manufacturing site without prejudice to future refiling.

4.4.3 US Distribution

Distribution for the US will take place from the ZENECA Pharmaceuticals facility in Newark Delaware.

Geographically the ZENECA Pharmaceuticals Group facility is on the Delaware Peninsula where the weather is moderated by both the Chesapeake Bay to the west and the Delaware River and Bay and Atlantic Ocean to the east, producing a temperate climate. The area of the plant site is a plain just south of hills which extend from northern Delaware into Pennsylvania.

The environment of the site itself is 87 acres of relatively flat second growth woodlands. The soils are a thin layer of organic soils over heavy clay and occasional sand or glacial till. The sedimentary rock beneath the soils is deeply buried at the plant site and nearby area. Development of the site is about 405,000 square feet of buildings which support the pharmaceuticals business, substantial grass lawn areas and decorative plantings, paved walkways, paved and unpaved access roads, and paved parking lots. The buildings are of modern construction, designs and materials and have been built specifically for pharmaceuticals production since 1971. Site drainage improvements have been made by installing a pond to slow rainwater run-off from buildings and paved areas.

The environment adjacent to the site is to the north, US interstate 95; to the west a casement for an interchange to US Interstate 95; to the south, Old Baltimore Pike and a residential area; and to the east, Salem Church Road and a residential area.

The potable water is supplied by Wilmington Suburban Company and the waste water from the site is treated in the New Castle County Municipal Sewer System at the Wilmington Treatment Facility.

SECTION 5. IDENTIFICATION OF CHEMICALS SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION

5.1 Drug Substance

The active drug substance zolmitriptan is also known as 311C90.

5.1.1 Complete Nomenclature

(S)-4-{[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl}-2-oxazolidinone

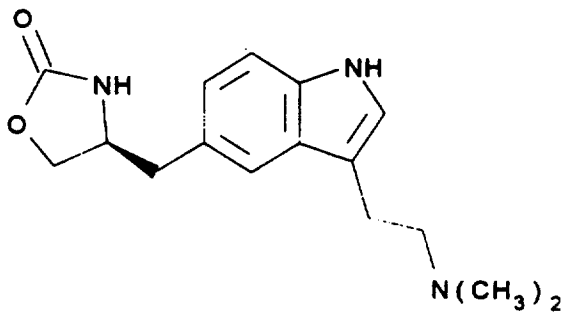
5.1.2 Chemical Formula

$C_{16}H_{21}N_3O_2$

5.1.3 CAS Registration Number

139264-17-8

5.1.4 Molecular Structure



5.1.5 Molecular weight

287.36

5.1.6 Physical Description

White to almost white powder

5.2 Intermediates in the Synthesis of zolmitriptan

A list of intermediates in the synthesis of zolmitriptan is included in Section 15.3

SECTION 6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Manufacture of the Active Drug Substance- Glaxo-Wellcome's Dartford Facility UK

All production of active pharmaceuticals on the Dartford Site is authorised by Her Majesty's Inspectorate of Pollution (HMIP) under the terms and conditions of the Environmental Protection Act and Integrated Pollution Control (IPC). This requires the site, as well as meeting all current operating consents and conditions, to employ the Best Available Techniques Not Entailing Excessive Costs (BATNEEC) to minimise all discharges to the environment. It is also required to utilise the Best Practical Environmental Option (BPEO) in minimising and disposing of wastes.

The Authorisation is numbered AK6853 (Variation Number AQ 2613) and the site's performance is continuously monitored by HMIP. Permission for the site to be allowed to continue to operate is dependant on continuing compliance with all the terms of the Authorisation.

A copy of the Authorisation is included in Section 15.4

Manufacture of zolmitriptan is carried out in eight stages as shown in Table 1. Below.

STAGE	PRODUCT
1	754W91
2	248W92
3	3701W92
4	3702W92
5	276C91
6	311C90 Crude
7	311C90 Recryst
8	311C90 Pure

Table 1 Manufacturing Stages for zolmitriptan

Wastes from the manufacture of zolmitriptan are treated by general systems on the site. Individual streams are combined into a number of component streams for disposal as follows:

Discharges to air
Aqueous wastes for discharge
Solid wastes
Solvent wastes for incineration

Process wastes are complex mixtures which have not been fully characterised. The composition of these streams will vary depending upon the current pattern of production on the site.

6.1.1 Releases into Air

Stage 1.
Gaseous releases from headers, reactor vents, pressure line transfer operations and hydrochloric acid gassing are directed to a recirculating scrubber unit containing 10% sodium hydroxide. The scrubber liquors are changed every batch.

Stage 2.
Gaseous releases from headers, reactor vents and pressure line transfer operations are directed to a recirculating scrubber unit containing 10% sodium hydroxide.

Stages 3 and 4.
Hydrogen is vented to atmosphere.
Ammonia operations in stage 4 are directed to scrubber tower unit containing water. The need to direct gaseous releases, containing Butanol from stages 3 and 4 is under review.

Stage 5.
Reactor reflux and distillation operations are directed to atmosphere.
Transfer of warm batch via filter and blowdown is directed to a scrubbing tower unit.

zolmitriptan production is manufactured in plant authorised by Her Majesty's Inspectorate of Pollution, authorisation number AK 6853 (Variation number AQ 2613).

The production of zolmitriptan is not expected to have an adverse impact on the current compliance the site.

6.1.2 Releases to Water

All scrubbing tower liquors are directed to the site's Effluent Collection Plant. Aqueous waste, including washes, filter washes and charcoal washes, are directed to the site's Trade Effluent Treatment Plant.

Waste directed to the site's Trade Effluent Collection Plant is pH adjusted and blended prior to release into the local sewer under consent of Thames Water Utilities (TWU) and as authorised by Her Majesty's Inspectorate of Pollution (HMIP). Effluent released into the sewer is mixed with domestic effluent prior to reception at a local TMU sewage treatment works where it is biologically degraded.

Wastewater is discharged from the site to the sewer under a licence granted by the Thames Water Utilities (licence number LS73008A) and under an authorisation granted by Her Majesty's Inspectorate of Pollution (Authorisation number AK 6853, Variation number AQ 2613). Copies of the TWU consent and HMIP Authorisation are included in Section 15.4

The production zolmitriptan is not expected to have an adverse impact on the current compliance of the site.

6.1.3 Solid waste

Solid waste will either be incinerated on-site in a solid incineration unit , HMIP Authorisation number AP 4874, or will be directed to an appropriately licensed landfill site or off site high temperature incineration facility.

A copy of Authorisation AP 4874 is included in Section 15.4

The landfill site used is:

Cory Environmental Ltd
Mucking Landfill site

A copy of the licence is included in Section 15.4

The small volume of these wastes will not materially increase the existing volume so the production of zolmitriptan is not expected to have an adverse impact on the environment.

6.1.4 Solvent Wastes for Incineration

Liquid waste containing solvent will be directed to the on-site liquid incineration unit. This is authorised by HMIP, Authorisation number AG 9264 (Variation AP 4874) a copy of which is included in Section 15.4
The amount of these wastes arising from the production of zolmitriptan are small and are not expected to have an adverse effect on the site's current compliance.

6.1.5 Effect of approval on compliance with current limits at the production site

The production of zolmitriptan will be controlled so as to ensure the site continues to meet all the relevant Agreements, Authorisations and Permits. There will be a minimal increase in the amount of materials discharged from the site which will be controlled using existing systems. The nature and amounts of these materials is such that they will be accommodated within the terms of the existing permits and authorisations.

6.1.6 Statement of Compliance

The Glaxo Wellcome manufacturing facility is in compliance with, or has an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of zolmitriptan at the Glaxo Wellcome Operations Dartford facility.

APPEARS THIS WAY
ON ORIGINAL

6.2 Formulation and Packing of Drug Product - Carolina Facility Puerto Rico

The site is fully permitted in accordance with Local and Federal Regulations. All emissions from the processing facilities are treated in accordance with local legislation and are within permitted levels.

6.2.1 Aqueous waste

All aqueous wastes from the formulation of zolmitriptan are transferred to the sites effluent system and the pH is adjusted. All waste waters are collected and routed to the PRASA (Puerto Rico Aqueduct and Sewer Authority) sewer system and treated at the Carolina Regional Wastewater Treatment Plant.

IPR's discharge is regulated by Industrial Wastewater Discharge Permit No. GDA-91-102-055 issued by PRASA.

It is estimated that less than 1.0 kg/year of zolmitriptan is discharged to the sewage system.

6.2.2 Air Emissions

Emission controls employed during the manufacturing process will result in insignificant emissions of particulate matter. The plant employs bag filters in fluid bed dryers to control the atmospheric release of total particulate from the manufacturing process. A central vacuum system collects dust and solids from plant cleaning. Specific ventilation systems include ventilation for mixing and drying, blending compression and packing.

All emissions to air are regulated by Air Emission Permit No PFE-LC-16-1295-1644-I-II-0 issued by the Puerto Rico Environmental Quality Board.

6.2.3 Solid Wastes

All solid wastes are collected as part of a site wide system and stored temporarily, in appropriate containers, in a specially designated area.

All wastes are transported by licensed contractors to an approved incineration facility. This facility operates under a permit issued by the local authority and meets all relevant operating and discharge consents.

All contractors are audited by IPR.

6.2.4 Permits

Storm Water General Permit issued 31 Dec. 1992
Permit No. PRR00A115

Resource Conservation and Recovery Act issued 27 Feb. 1987
Permit No. PRD981874746

Air Emission Permit renewed 24 Jan. 1995
Permit No. PFE-LC-16-0194-0025-I-II-0

Industrial Waste Water Permit issued 1 Sept. 1991
Permit No. GDA-91-102-055

Bio-Medical Waste Permit issued 11 Dec. 1991
Permit No. DBM-16-09-0007-R-95

6.2.5 Effect of Approval on Compliance with Current Limits at the Production Site

The formulation of the zolmitriptan drug product will be controlled so as to ensure the site continues to meet all the relevant Agreements, Authorisations and Permits. There will be a minimal increase in the amount of materials discharged from the site which will be controlled using existing systems. The nature and amounts of these materials is such that they will be accommodated within the terms of the existing permits and authorisations

The local permitting authorities have been informed of the proposal to formulate zolmitriptan and have agreed to the proposals.

6.2.6 Compliance Statement

IPR states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of zolmitriptan at its facilities in Carolina, Puerto Rico, as well as emission requirements set forth in applicable Federal, State and local statutes, and regulations.

6.3 Formulation of the Drug Product at Glaxo Wellcome's facility at Dartford

Reference is made to the February 28, 1997 submission to the ZOMIG NDA 20-768 in which Zeneca Pharmaceuticals notified the Agency, that pursuant to 21 CFR 314.65, the Glaxo Wellcome facilities in Dartford, United Kingdom has been withdrawn from the subject NDA as a commercial drug product manufacturing site without prejudice to future refiling.

6.3.1 Effect of approval on compliance with current limits at the production site

The formulation of the zolmitriptan drug product will be controlled so as to ensure the site continues to meet all the relevant Agreements, Authorisations and Permits. There will be a minimal increase in the amount of materials discharged from the site which will be controlled using existing systems. The nature and amounts of these materials is such that they will be accommodated within the terms of the existing permits and authorisations.

6.3.2 Statement of Compliance

The Glaxo Wellcome manufacturing facility is in compliance with, or has an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of the zolmitriptan drug product at the Glaxo Wellcome Operations Dartford facility.

6.4 Distribution - Newark, Delaware

The site is fully permitted in accordance with Local, State and Federal Regulations. All emissions from the processing and distribution facilities are treated in accordance with local legislation and are within permitted levels. Emissions to the environment consist of solid wastes due to packaging materials, such as paper and plastics, any rejected or returned product and aqueous wastes arising from cleaning.

Distribution of zolmitriptan will be carried out in existing areas used for the warehousing and distribution of pharmaceuticals It will not involve any new construction or major building modifications.

6.4.1 Aqueous waste

Entry of the drug product into the wastewater is only incidental to the cleaning of the facility. All aqueous wastes are transferred to the sites effluent system. The total effluent from the site is discharged to the New Castle County Municipal Sewer System and treated at the Wilmington Delaware Plant. All discharges to the treatment plant are made under an agreement between Zeneca and the local Waste Authority.

6.4.2 Air emissions

There will be no emissions to air resulting from the distribution of zolmitriptan.

6.4.3 Solid wastes

All solid wastes are collected as part of a site wide system and stored temporarily, in appropriate containers, in a specially designated area prior to disposal by licensed contractors.

All wastes that have come in contact with or potentially have come in contact with the active ingredient are transported by licensed contractors to an approved incineration facility. This facility operates under a licence from the local authority and meets all relevant operating and discharge consents.

The contractors currently used by ZENECA are:

Lancaster County Solid Waste
Management Authority Resource
Recovery Facility
Route 441 South
Bainbridge, PA 17502

All contractors are audited by Zeneca.

6.4.4 Permits

Waste Water Permit

Departmental of Public Works of New Castle County Number #WDP-76-025.

Hazardous waste generator permit

United States Environmental Protection Agency. Number DED0547431909

Air permits

Departmental of Natural Resources and Environmental Resources of the State of Delaware and are as follows:

Permit #	Name
80-0863	Steam Boiler #1
80-0864	Steam Boiler #2
80-0872	Sorbitrate Dust Collector
81-0049	Pilot Plant Granulator
81-1017	Sorbitrate Granulator
82-0961	Nolvadex Dust Collector
82-0962	Nolvadex Granulator
82-0963	Nolvadex Vacuum System
82-0964	Tenormin Vacuum System
82-0965	Tenormin Granulator
82-0966	Tenormin Dust Collector
88-0010	Steam Boiler #3
89-0110	Pilot Plant Dying Oven Exhaust
89-0123	Pilot Plant Coating Pan Exhaust
89-0155	Liquid Manufacturing Dust Collector
90-0015	Packaging Dust Collector
91-0596	Pilot Plant Dust Collector

6.4.5 Effect of approval on compliance with current limits at the production site

The distribution of the zolmitriptan drug product will be controlled so as to ensure the site continues to meet all the relevant Agreements, Authorisations and Permits. There will be a minimal increase in the amount of materials discharged from the site which will be controlled using existing systems. The nature and amounts of these materials is such that they will be accommodated within the terms of the existing permits and authorisations.

6.4.6 Compliance Statement

ZENECA Pharmaceuticals, a Business Unit of ZENECA Inc., states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of zolmitriptan at its facilities in Newark, Delaware, as well as emission requirements set forth in applicable Federal, State and local statutes, and regulations.

6.5 Expected Introduction Concentration (EIC)

Due to the strict controls during the production of the drug substance and manufacture and packing of the drug product little material will enter the environment. Introduction of Zomig into the environment will principally occur from use of the drug product.

The EIC has been calculated a described in Section 15.1

As the EIC is less than 1ppb the assessment meets the criteria for Tier 0.

APPEARS THIS WAY
ON ORIGINAL

SECTION 7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

No information submitted

SECTION 8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

No information submitted

SECTION 9. USE OF RESOURCES AND ENERGY

No information submitted

SECTION 10. MITIGATION MEASURES

No information submitted

SECTION 11. ALTERNATIVES TO PROPOSED ACTION

No information submitted

SECTION 12. PREPARERS

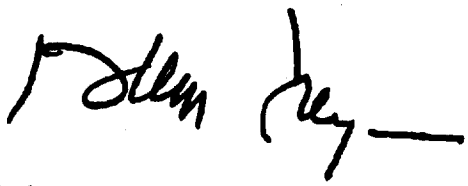
This assessment was prepared by :

1) Martin Rackham, Occupational Hygiene and Environmental Affairs Manager, ZENECA PHARMACEUTICALS. He has a Bachelors Degree in Chemistry and Physiology and a Masters Degree in Occupational Hygiene.

2 Russell Thompson, Environmental Protection Manager, Glaxo-Wellcome. He has a Batchelors Degree in Chemistry and a Diploma in Hazardous Waste Management

SECTION 13. CERTIFICATION

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



Rubén Freyre BSc CQE
President and General Manager
IPR Pharmaceuticals, Inc.

SECTION 14. REFERENCES

1.Guidance for the submission of an environmental assessment in human drug applications and supplements.

Centre for Drug Evaluation and Research November 1995.

2. Guidance on Preparation of Environmental Assessments

Pharmaceutical Manufacturers of America

15. APPENDICES

15.1 Calculation of Expected Introduction Concentration (EIC)

It is estimated that at peak sales the amount of zolmitriptan entering the United States will be in the order of

15.2 Material Safety Data Sheet for Zomitriptan

ZENECA Pharmaceuticals

MATERIAL SAFETY DATA SHEET

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Name: ZOLMITRIPTAN

Address/Phone No. : IPR Pharmaceuticals, Inc.
P.O. Box 10000
Guayama, Puerto Rico 00785
Tel (Business) : (787) 866-1290

Alternative Names
ZOMIG
ZD8250
311C90
(S)-4-((3-(2-(Dimethylamino)ethyl)-IH-indol-5-yl)methyl)
-2-oxazolidinone

2. COMPOSITION/INFORMATION ON INGREDIENTS

CAS No. : 139264-17-8
Use : serotonin subtype 1D/B receptor agonist

HAZARDOUS INGREDIENT(S)	CAS No.
Zolmitriptan	139264-17-8

3. HAZARDS IDENTIFICATION

Form : powder
Color : white

Caution - Substance not yet fully tested
Harmful if swallowed.
May cause sedation.

ZENECA Pharmaceuticals

MATERIAL SAFETY DATA SHEET

Name: ZOLMITRIPTAN

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4. FIRST-AID MEASURES

Inhalation : Remove patient from exposure, keep warm and at rest. Obtain medical attention.

Skin Contact : Remove contaminated clothing. Wash skin with soap and water. If symptoms (irritation or blistering) occur obtain medical attention.

Eye Contact : Irrigate with eyewash solution or clean water, holding the eyelids apart, for at least 15 minutes. Obtain medical attention.

Ingestion : Wash out mouth with water. Obtain medical attention.

Note to Physicians
This information is based on overdosage of the final product.

There is no specific antidote to Zolmitriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

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5. FIRE-FIGHTING MEASURES

Flammable Properties

Flammable Powder Class	: A
Minimum Ignition Temperature (Deg C/Deg F)	: 400-450/752-842
Minimum Ignition Energy (mJ)	: 10-30

Group A dust. The material can form flammable dust clouds in air.
Combustion will evolve toxic vapors.
Thermal decomposition will evolve flammable vapors.

Extinguishing Media
water spray, foam, dry chemical or CO2.

Fire Fighting Instructions
A self contained breathing apparatus and full protective clothing should be worn in fire conditions.

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6. ACCIDENTAL RELEASE MEASURES

Clear up spillages. Ensure suitable personal protection during removal of spillages.
Wash the spillage area with water, and flush to a sewer serviced by a wastewater treatment facility.
Transfer to a container for disposal or recovery. Do not allow to enter drains, sewers or watercourses.

7. HANDLING AND STORAGE

7.1 HANDLING

Do not breathe dust. Avoid contact with skin and eyes.
Use extraction and ventilation arrangements.

Follow procedures specified in the National Fire Protection Association Codes and Standards for handling combustible dusts. (or explosive dusts)

7.2 STORAGE

Keep container tightly closed. Keep container in a well ventilated place. Keep away from direct sunlight.

Storage Temperature : Keep at a temperature not exceeding 25 Deg C
Storage Life : 2 year(s) at 30 Deg C

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Engineering Controls
Occupational Exposure Limits

HAZARDOUS INGREDIENT(S)	TWA ppm	TWA mg/m3	STEL/CEILING (C) ppm	STEL/CEILING (C) mg/m3	
Zolmitriptan	-	0.32	-	-	COM (Provisional)

MATERIAL SAFETY DATA SHEET

Name: ZOLMITRIPTAN

Personal Protective Equipment

Wear suitable respiratory protective equipment if exposure to levels above the occupational exposure limit is likely. Wear suitable gloves and eye/face protection.

Respirators	**: Use NIOSH respirator approved for dusts with a TLV greater than 0.05 mg/m3.**
Protective Clothing	**: Impervious gloves and apron.**
Eye Protection	**: Chemical tight goggles.**
Other Protective Equipment	**: Eyewash station and safety shower in work area.**

9. PHYSICAL AND CHEMICAL PROPERTIES

Form	: powder
Color	: white
Melting Point (Deg C/Deg F)	: 135-140/275-284
Solubility (Water)	: slightly soluble
Partition Coefficient	: -1.34

Dissociation constant: 9.64

10. STABILITY AND REACTIVITY

Incompatible materials: formaldehyde, alkalis

11. TOXICOLOGICAL INFORMATION

Inhalation	: Adverse effects similar to ingestion may occur following exposure to the dust.
Skin Contact	: No information available.
Eye Contact	: No information available.
Ingestion	: Harmful if swallowed. Oral Median Lethal Dose 1000-1500mg/kg (rat). May cause sedation.

Long Term Exposure : Studies in animals have shown that high doses produce adverse effects on the thyroid gland.
Some evidence of genotoxicity but unlikely to present a carcinogenic hazard to man.
Studies in animals have shown that exposures produce no teratogenic effects.

12. ECOLOGICAL INFORMATION

Environmental Fate and Distribution
The substance is essentially insoluble in water.
The substance has low potential for bioaccumulation.
The substance has low mobility in soil.

Persistence and Degradation
The substance is partially biodegradable in soil. There is no evidence of hydrolysis in water.

Toxicity
EC50 (Daphnia magna) (24 hour) 380mg/L
EC50 (Daphnia magna) (48 hour) 250mg/L
EC0 (Daphnia magna) (24 hour) 130mg/L

Effect on Effluent Treatment
Biological Oxygen Demand (BOD 28 DAY) 0% (sludge)
There is evidence of inhibition to the aerobic treatment process at a concentration (mg/l) of 1728 (30 min), 1080 (3 hour)

Effect on Atmospheric Ozone
No information available.

13. DISPOSAL CONSIDERATIONS

Incinerate under approved controlled conditions, using incinerators suitable for the disposal of noxious chemical waste.
Disposal should be in accordance with local, state or national legislation.

Disposal Method
Discarded product is not a hazardous waste under RCRA, 40 CFR 261.

Container Disposal
When empty, container may contain product residue and flammable vapors.
Observe all hazard precautions.

ZENECA Pharmaceuticals

MATERIAL SAFETY DATA SHEET

Name: ZOLMITRIPTAN

14. TRANSPORT INFORMATION

Not Classified as Dangerous for Transport.

15. REGULATORY INFORMATION

TSCA (Toxic Substances Control Act) Regulations, 40 CFR 710:
This product is a drug and is exempt from TSCA regulation.

CERCLA and SARA Regulations (40 CFR 355, 370 and 372):
This product does not contain any chemicals subject to the reporting requirements of SARA Section 313.

16. OTHER INFORMATION

This Material Safety Data Sheet was prepared in accordance with ANSI Standard Z400.1, 1993.

The following sections contain revisions or new statements: 1,12

GLOSSARY

COM : The company aims to control exposure in its workplace to this limit This is an in-house standard for the active ingredient handled during manufacture
TLV : The company aims to control exposure in its workplace to the ACGIH limit
Sk : Can be absorbed through skin
Sen : Capable of causing respiratory sensitization

The information herein is given in good faith but no warranty, expressed or implied, is made.