CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20639

CHEMISTRY REVIEW(S)

Apr 1 1997

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-639

CHEM. REVIEW # 3

REVIEW DATE 24-MAR-97

SUBMISSION TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED DATE**
ORIGINAL	29-JUL-96	30-JUL-96	
AMENDMENT N(BC)	27-FEB-97	28-FEB-97	06-MAR-97

NAME AND ADDRESS OF APPLICANT

ZENECA Limited - Macclesfield, England
US Agent - Zeneca Pharmaceuticals
1800 Concord Pike, PO Box 15437
Wilmington, DE 19850-5437

DRUG PRODUCT NAME
Proprietary: **SEROQUEL®** Tablets
Nonproprietary/USAN: quetiapine fumarate
Code Name/Number: ICI 204,636; ZD 5077; ZD 204,636
Chem. Type/Ther. Class:

PHARMACOLOGICAL CATEGORY/INDICATION Antipsychotic
DOSAGE FORM Tablets
STRENGTHS 25, 100, and 200 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
IUPAC: Bis [2-(2-[4-(dibenzo[b,f][1,4]thiapin-11-yl)piperazin-1-yl]ethoxy)ethanol], fumarate
CAS: Ethanol[2-(2-[4-(dibenzo[b,f][1,4]-thiazepin-11-yl-1)piperazinyl)ethoxy]-(E)-2-butenedioate (2:1)

$C_{21}H_{25}N_3O_2S$ (base) Mol. Wt. 883.1 (383.5 + 116.1)

CAS Registry #: 111974-69-7 (base)
111974-72-2 (fumarate salt)

SUPPORTING DOCUMENTS: IND

RELATED DOCUMENTS: US Pat. No. 4,879,288 (exp. March 20, 2007), Zeneca Ltd., Macclesfield, Cheshire, UK

CONSULTS: The CGMP compliance status of the manufacturing facilities is ACCEPTABLE as of 15-JAN-97. The proposed trademark "SEROQUEL" is ACCEPTABLE by the CDER Labeling and Nomenclature Committee. The MV package is in preparation. The review of the amended EA is pending (HFD-357).
REMARKS/COMMENTS: The NDA is amended to support coated tablets as the to-be-marketed formulation. The 1X batch has ben determined as based on the sizes of clinical/stability batches of the 25 mg tablets. The 36 months' expiration dating period proposed for SEROQUEL Tablets is not justified by the data provided in the NDA (i.e., 24 months of data for 2 pilot scale batches and 18 months for 2 commercial scale batches).

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-639, as amended, be APPROVED with a 24 months expiration dating period. We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-639
HFD-120
HFD-120/MGuzewska
HF-120/SHardeman/CSO
HFD-120/SBlum
R/D Init by: SWB

SWB 4/4/97

M. Guzewska

M. Guzewska, Ph.D., Chemist

Filename: n20639.003

APR 11 1997

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-639

CHEM. REVIEW # 2

REVIEW DATE 19-MAR-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	29-JUL-96	30-JUL-96	
AMENDMENT N(BC)	20-SEP-96	25-SEP-96	28-SEP-96
AMENDMENT N(BC)	30-SEP-96	04-OCT-96	08-OCT-96
AMENDMENT N(BC)	03-OCT-96	11-OCT-96	13-OCT-96
AMENDMENT N(BC)	16-OCT-96	21-OCT-96	23-OCT-96
AMENDMENT NC	27-NOV-96	06-DEC-96	11-DEC-96

NAME AND ADDRESS OF APPLICANT

ZENECA Limited - Macclesfield, England
US Agent - Zeneca Pharmaceuticals
1800 Concord Pike, PO Box 15437
Wilmington, DE 19850-5437

DRUG PRODUCT NAME
Proprietary: **SEROQUEL®** Tablets
Nonproprietary/USAN: quetiapine fumarate
Code Name/Number: ICI 204,636; ZD 5077; ZD 204,636
Chem. Type/Ther. Class:

PHARMACOLOGICAL CATEGORY/INDICATION Antipsychotic
DOSAGE FORM Tablets
STRENGTHS 25, 100, and 200 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

IUPAC: Bis [2-(2-[4-(dibenzo[b,f][1,4]thiapin-11-yl)piperazin-1-yl]ethoxy)ethanol], fumarate

CAS: Ethanol[2-(2-[4-(dibenzo[b,f][1,4]-thiazepin-11-yl-1)piperazinyl)ethoxy]-(E)-2-butenedioate (2:1)

$C_{21}H_{25}N_3O_2S$ (base) Mol. Wt. 883.1 (383.5 + 116.1)

CAS Registry #: 111974-69-7 (base)
111974-72-2 (fumarate salt)

SUPPORTING DOCUMENTS: see Review #1

RELATED DOCUMENTS: see Review #1

CONSULTS: The CGMP compliance status of the manufacturing facilities is ACCEPTABLE as of 15-JAN-97. The proposed trademark "SEROQUEL" is ACCEPTABLE by the CDER Labeling and Nomenclature Committee. The MV package will be prepared after the resubmission of the Drug Product section of the NDA . The review of the amended EA is pending (HFD-357).
REMARKS/COMMENTS: This review consists of two parts: Part I contains additional information on the N.D.S. and the drug product previously submitted via several facsimiles, and Part II presents Zeneca's responses to the CM&C Deficiency Letter. The information contained in Part I of the review pertains to the tablets with a coating, the formulation described in the original NDA submission. This information will be amended again to reflect the planned by Zeneca change to the coating level.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-639, as amended, NOT APPROVABLE because of lack of evidence of stability for the tablets with a coating (the product described in the original NDA submission). Zeneca plans to amend the NDA and propose the coated tablets as the to-be-marketed formulation.

cc: Orig. NDA 20-639
HFD-120
HFD-120/MGuzewska
HF-120/SHardeman/CSO
HFD-120/SBlum
R/D Init by: SWB

3/28/97

M. Guzewska, Ph.D., Chemist

Filename: n20639.002

Consult #675 (HFD-120)

SEROQUEL quetiapine fumarate 25, 100, 200 mg tablets

The Committee found no look-alike/sound-alike conflicts nor any misleading and fanciful aspects with the proposed proprietary name. The consult submitter was concerned with a similarity with "Sequel", Lederle's trademarked term for their extended release products. However, this term is not used by itself in practice and is always used in conjunction with a product proprietary name, therefore the LNC felt there was little chance for confusion.

The LNC has no reason to find the proposed name unacceptable.

D U Boring 10/18/96, Chair
CDER Labeling and Nomenclature Committee

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20639

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

SEROQUEL®

(quetiapine fumarate)

Tablets 25, 100, or 200 mg

NDA 20-639

Division of Neuropharmacological Drug Products (HFD-120)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

SEROQUEL®

(quetiapine fumarate)

Tablets 25, 100, or 200 mg

NDA 20-639

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 SEROQUEL®, ZENECA Limited has prepared an environmental assessment in accordance with 21 CFR 25.31a in the Tier 0 format (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Quetiapine is a chemically synthesized drug which is administered as 25, 100, or 200 mg tablets in the manifestations psychotic disorders. The drug substance is manufactured by ZENECA GmbH, Germany with intermediates made by ZENECA Limited, England. The active drug substance is formulated into drug product and packaged by ZENECA Pharmaceuticals, Delaware. The finished drug product will be used in hospitals, outpatient therapy and individuals throughout the USA.

Quetiapine 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 Assessment in Human Drug Applications and Supplements.*

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed high temperature incineration. 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.

4/10/97 S G Vincent
DATE

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

4/10/97 Nancy S Sager
DATE

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

Attachments: Environmental Assessment

SECTION 1.

DATE: **APRIL 1996**

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SECTION 2.

APPLICANT

ZENECA Limited,
Macclesfield, Cheshire, England
ZENECA Pharmaceuticals a business unit of ZENECA Inc. is the authorised US agent for ZENECA Limited for the subject NDA

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SECTION 3.

ADDRESSES

Administrative Headquarters.

ZENECA Limited
Alderley Park
Macclesfield Cheshire
SK10 4TF
England

Site for Manufacture of Chemical Intermediates

ZENECA Limited
Avlon Works
Severnside Site
Bristol BS10 7SJ
England

Site for Purification of Active Agent

ZENECA GmbH
Otto-Hahn Strasse
68723 Plankstadt
Germany

Site for Manufacture of the Drug Product

ZENECA Pharmaceuticals
587 Old Baltimore Pike
Newark, Delaware 19702

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

ZENECA Limited is filing a new drug application for approval to manufacture and formulate, package and distribute SEROQUEL.

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

The NDA number is 20-639

SEROQUEL is formulated as tablets containing 25, 100 or 200 mg of the active drug substance which is also known as quetiapine fumarate (ICI 204,636).

The drug product is packaged in strips of PVC/aluminium foil blisters. These are contained in a cardboard carton which also contains the patient information leaflet.

4.2 Describe the need for the proposed action

SEROQUEL is a new drug for the management of the manifestations of psychotic disorders.

4.3 Locations where the products are to be :-

4.3.1 Produced

The active material will be produced at the ZENECA manufacturing site at Plankstadt in Germany.

The address of the facility is:-

ZENECA GmbH
Otto-Hahn Strasse
68723 Plankstadt
Germany

Intermediates will be produced at the ZENECA manufacturing site at Bristol.

The address of the facility is:-

ZENECA Limited
Avlon Works
Severnside Site
Bristol BS 10 7SJ
England

4.3.2 Formulated

The active drug substance will be formulated at the ZENECA facility at Newark, Delaware in the USA

The address of the facility is:-

ZENECA Pharmaceuticals
587 Old Baltimore Pike
Newark, Delaware 19702

4.3.3 Final Packaging

Final packing will take place at Newark, Delaware in the USA.

The latter facility will be the distribution centre for the USA.

4.3.4 Used

SEROQUEL is indicated for the management of the manifestations of psychotic disorders. The product will be used in hospitals and in outpatient therapy. The product will be used by individuals throughout the USA.

4.3.5 Disposed

The product is used in hospitals and homes for treating patients with psychotic disorders. 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.

The fate of wastes arising from production activities and any materials returned to the sites of production are described in Section 6

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

4.4.1 Production of chemical intermediates

The site at Bristol is located in an area designated as an industrial zone. The area of the site is approximately 98,000m^2. It stands on a plain just to the west of a range of hills which run north to south. The climate is temperate and the predominant wind direction is from the south west.

The site stands on alluvial deposits from the river Severn over a clay base. The soil is sandy with many small pebbles. It is bounded by other industrial property and farmland.

The site has been developed over the last 20 years for the production of bulk pharmaceutical materials and their intermediates.

The buildings are of modern design and construction.

4.4.2 Site for manufacture of active material

The site at Plankstadt is located in an area designated as an industrial zone. The area of the site is approximately 95,000 m^2. It stands on a plain just to the west of a range of hills which run north to south. The climate is temperate and the predominant wind direction is from the west. The site stands on alluvial deposits from the rivers Rhein and Neckar. The soil is sandy with many small pebbles. It is bounded by other industrial property and farmland.

The site has been developed over the past 20 years to provide facilities for the purification of active materials and the formulation and packing of pharmaceuticals products. The buildings are of modern design and construction.

4.4.3 Sites of formulation facilities

4.4.3.1 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 supports 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.

4.4.4 Sites for final packing and distribution

Final Packing and distribution will take place at Newark, Delaware in the US

The site is described in 4.4.3.1

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SECTION 5.

IDENTIFICATION OF CHEMICALS SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION

5.1 Drug Substance

The active drug substance is also as quetiapine fumarate (ICI 204,636).

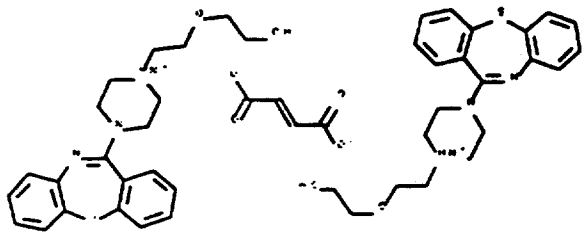
5.1.1 Complete Nomenclature

bis 2-(2-[4-dibenzo[b,f] [1,4]- thiazepin - 11-yl) piperazin -1-yl] ethoxy) ethanol] fumarate

5.1.2 CAS registration number

111974-72-2

5.1.3 Molecular structure



5.1.4 Molecular weight

883.1 (fumarate salt)

5.1.5 Molecular formula

$C_{46}\ H_{54}\ O_8\ N_6\ S_2$

5.2 Physical description

Fine, white to off white powder

5.3 Materials used in the synthesis

A list of materials used in the synthesis of ICI 204,636 is included in Section 15.3

5.4 Impurities

The impurities in the drug product are:

ICI 204,636 Des Ethanol
ICI 204,636 ARP

All impurities are controlled to a level less than 0.5% w/w in total.

CAS Numbers have not been allocated to these materials.

These materials are of similar chemical structure to ICI 204,636 so that an assessment of the properties of ICI 204,636 will provide an adequate assessment of any potential effect on the environment.

5.5 Additives

The drug substance contains no additives.

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SECTION 6.

INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 From production of intermediates for the drug substance (ICI 204,636) at Avlon Site

All production of intermediates for active pharmaceuticals on the Avlon 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 AL6794 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

Wastes from the manufacture of ICI 204,636 are treated by general systems on the site. Individual streams are combined into a number of component streams for disposal as follows:

Aqueous wastes for discharge
Aqueous wastes unsuitable for discharge before further treatment
Non aqueous solvent wastes for recovery
Solvent wastes for incineration
Solid 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 Aqueous arisings from manufacture of intermediates of ICI 204,636

Aqueous layers from the production of drug intermediates are combined in the sites effluent collection/ treatment system. The total effluent from the site is settled to remove solids and the pH adjusted to between 6.0 - 10 before being discharged to the river Severn under conditions specified in the Authorisation.

Her Majesty's Inspector of Pollution and the National Rivers Authority have been informed of the intention to manufacture ICI 204,636 and have not seen it necessary to impose any specific limits for emissions from the ICI 204,636 process.

Aqueous Liquid Wastes which are not suitable for direct discharge are treated by contractors to make them suitable for discharge to the environment. The facility currently used by ZENECA is

Leigh Environmental Ltd
Stubbins Green Road
West Midlands
England

Leigh Environmental Ltd are authorised by Her Majesty's Inspector of Pollution. The number of the Authorisation is SL 167.

All contractors are regularly audited by ZENECA.

6.1.2 Non-aqueous liquid wastes

Non-aqueous liquid wastes are segregated where possible into separate components. These components are transported to specialised operators for recovery for non-pharmaceutical use. Where segregation and recovery is not feasible the streams are collected together in a common site system for high temperature incineration in a licensed facility off-site.

In this facility a destruction efficiency of >99.99% is assumed for all organic species. The flue gasses are treated to remove pollutants prior to discharge to atmosphere. The treatment consists of rapid quenching of the stream to minimise secondary reactions followed by wet scrubbing and particulate removal. The facility meets all relevant operating and discharge permits.

The facility currently used by ZENECA is

Rechem Ltd
New Road
Pontypool
Panteg
Gwent
Wales

Rechem Ltd is authorised by Her Majesty's Inspectorate of Pollution. The authorisation number is AG 7946

All contractors are regularly audited by ZENECA.

6.1.3 Treatment of solid waste arisings from the production of intermediates for ICI 204,636

All solid wastes are collected as part of a site-wide system and stored temporarily, in appropriate containers, in a specially designated area. The storage and treatment of the wastes are controlled as part of the site's Authorisation

All organic wastes are transported, by licensed carriers, to an off-site facility for high temperature incineration.

In this facility a destruction efficiency of >99.99% is assumed for all organic species. The flue gasses are treated to remove pollutants prior to discharge to atmosphere. The treatment consists of rapid quenching of the stream to minimise secondary reactions followed by wet scrubbing and particulate removal. The facility meets all relevant operating and discharge permits.

The facility currently used by ZENECA is

Rechem Ltd
New Road
Pontypool
Panteg
Gwent

Rechem Ltd is authorise by Her Majesty's Inspectorate of Pollution. The authorisation number is AG 7946

All contractors are regularly audited by ZENECA.

6.1.4 Air emissions

All air emissions from the manufacturing facilities are in compliance with local and national legislation.

6.1.5 Control of air emissions

Emissions from ICI 204,636 production are discharged in such a manner as to comply with local legislation. Where appropriate emissions are discharged through scrubbers or are controlled by installing cooled condensers on reactors.

Monitoring to ensure compliance is carried out where specified in the Authorisation or where deemed appropriate by the site's management.

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

The production of intermediates for ICI 204,636 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 relevant authorities have been informed of the proposals to manufacture intermediates for ICI 204,636 and have raised no objection or imposed any additional conditions.

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6.2 Purification of drug substance at Plankstadt

All emissions from the processing facilities at Plankstadt are treated in accordance with local legislation.

6.2.1 Aqueous waste

All aqueous wastes from the purification of ICI 204,636 are transferred to the sites effluent system. The total effluent from the site is settled to remove solids and the pH adjusted to between 6.5-8.5 before being discharged to the local sewerage treatment plant. All discharges to the treatment plant are made under an agreement between ZENECA and both the Landratsamt Heidelberg and Gemeinde Plankstadt.

It is estimated that less than 100kg/year of ICI 204,636 is discharged to the sewage system.

6.2.1.1 Major requirements of the Agreement:-

Flow	7763 cubic meters/week
TOD	2058 mg/l
pH	6.5-8.5
Temperature	$< 35^{0}C$
Heavy metals (Cu, Pb)	each less than 1ppm
(Zn)	2ppm
Hg	0.05 ppm

6.2.2 Other liquid emissions

Where liquid wastes are unsuitable for treatment in sewage treatment facilities they are sent for treatment in a facility approved by the Authorities

The contractors currently used by ZENECA are:

GVS GmbH and Company KG
Otto Hahn Strasse 50
68169 Mannheim
Germany

GVS GmbH and Company KG is authorised by the Stadt Mannheim

The permit number is: H 210099

6.2.3 Solid wastes

All solid wastes, such as used filters 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 licence from the local authority and meets all relevant operating and discharge consents.

The contractors currently used by ZENECA are:

GVS GmbH and Company KG
Otto Hahn Strasse 50
68168 Mannheim

GVS GmbH and Company KG is authorised by the Stadt Mannheim. The permit number is 9601387.

6.2.4 Air emissions

All discharges from the plant are either filtered or passed through adsorbers to prevent the discharges from the ICI 204,636 process. The aqueous effluent from the adsorbers is sent for incineration at licensed contractors. Used filters are sent for incineration at a facility approved by the Authorities as part of the site's system for disposing of solid wastes.

The contractors currently used by ZENECA are:

GVS GmbH and Company KG
Otto Hahn Strasse 50
68169 Mannheim
Germany

GVS GmbH and Company KG is authorised by the Stadt Mannheim

The relevant permit numbers is H210116

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

The production of the ICI 204,636 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. This will have no impact on compliance with current environmental legislation and permits.

A compliance statement is appended.

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REGIERUNGSPRÄSIDIUM KARLSRUHE

Eingegangen
13. OKT. 1995
Abt. SHE

Regierungspräsidium Karlsruhe · Postfach 8343 · 76035 Karlsruhe

Firma ZENECA
Postfach 20 80

68721 Schwetzingen

Korrespondenz-Adresse: Postfach 8343
76035 Karlsruhe

Liefer-Adresse: Schloßplatz 1-3
76131 Karlsruhe

Ihr Zeichen, Schreiben vom	Unser Aktenzeichen: (bitte bei Antwort angeben)	Bearbeiter/-in ☎(0721) 926- 6557	Karlsruhe
UV/Schü 29.09.1995	72b1-8823.12/4.1	Fr.Dr.Bertsch	05.10.1995/St

"Umweltbewertung" zur Vorlage bei der amerikanischen Food and Drug Administration (FDA)

Sehr geehrte Damen und Herren,

die Reinigung des Produktes Seroquel in der bestehenden Wirkstoffreinigungsanlage wurde mit Schreiben vom 18.01.1995 angezeigt.

Die Anlage zur Wirkstoffreinigung wurde mit der immissionsschutzrechtlichen Genehmigung des Landratsamtes Rhein-Neckar-Kreis vom 14.10.1976 und der immissionsschutzrechtlichen Änderungsgenehmigung des Regierungspräsidiums Karlsruhe vom 25.08.1993 genehmigt.

Nach den dem Regierungspräsidium Karlsruhe vorliegenden Erkenntnisse wird die Wirkstoffreinigungsanlage, in welcher der Wirkstoff Seroque gereinigt wird, derzeit entsprechend den behördlichen Genehmigungen des Regierungspräsidiums Karlsruhe betrieben.

Immissionsschutzrechtliche Genehmigungen werden auf Antrag (detaillierte Dokumentation) nach gründlicher Prüfung erteilt, wenn die in den einschlägigen Vorschriften genannten Genehmigungsvoraussetzungen

erfüllt sind. So bestimmt § 6 des Bundes-Immissionsschutzgesetzes, daß die Genehmigung zu erteilen ist, wenn

1. sichergestellt ist, daß die sich aus § 5 und einer aufgrund des § erlassenen Rechtsverordnung ergebenden Pflichten erfüllt werden und

2. andere öffentlich-rechtliche Vorschriften und Belange des Arbeitsschutzes der Errichtung und dem Betrieb der Anlage nicht entgegen stehen.

Mit freundlichen Grüßen

Usbeck-Ernst

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Regional Council Karlsruhe

5.10.1995

"Environmental assessment" for submission to American Food and Drug Administration (FDA)

Dear Sir/Madam,

The purification of the product Seroquel in the existing purification plant was reported in your letter of 18.1.1995.

The purification plant was given official approval 14.10.1976 by the administative offices of the Rhine-Neckar district in respect of emission control and official approval for changes in respect of emission control was given on 25.8.1993 by the Regional Council, Karlsruhe.

According to the knowledge available to the Regional Council, Karlsruhe, the purification plant, in which the active ingredient Seroquel is purified, is currently being operated in line with the official approval of the Regional Council, Karlsruhe.

Approvals regarding emission control are granted on request (detailed documentation) after thorough examination when the relevant regulations covering approval requirements have been met. Paragraph 6 of the federal emission control law states that approval can only be given when:

1. it is ensured that the obligations in para. 5 and enacted statutory order on the basis of para.7 can be satisfied and

2. other public-legal regulations and interests of maintenance of industrial health and safety standards of the implementation and operation of the plant do not conflict.

Yours sincerely,

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6.3 Formulation of the drug substance

6.3 Formulation of drug product - Newark, Delaware

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

Manufacture of SEROQUEL will be carried out in existing areas used for the manufacture of pharmaceuticals It will not involve any new construction or major building modifications.

6.3.1 Aqueous waste

Entry of the drug product into the wastewater is only incidental to the cleaning of the production equipment and room surfaces. All aqueous wastes from the formulation of SEROQUEL 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.

It is estimated that less than 20kg/year of SEROQUEL is discharged to the sewage system.

6.3.2 Air emissions

All discharges from the plant are filtered through high efficiency filters in accordance with local legislation and monitored as appropriate. The emission controls employed during the manufacturing process will result in insignificant particulate matter emissions.

6.3.3 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.

6.3.4 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

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

The formulation of the SEROQUEL 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.

6.3.6 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 SEROQUEL 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 SEROQUEL into the environment will principally occur from use of the product.

The EIC has been calculated as described in Section 15.1

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

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ZENECA

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Alderley Park
Macclesfield
Cheshire SK10 4TF
England

Telephone 01625 582828
Telex 669095 669388 ZENPHA C
Fax-Main 01625 585022 582572
Fax-Department 01625

TO WHOM IT MAY CONCERN

ENVIRONMENTAL IMPACT STATEMENT

This is to certify that Zeneca Limited of Macclesfield, Cheshire, England, being the manufacturer of 'Seroquel' at our site at Avlon Works, Severnside Site, Hallen, Bristol in the United Kingdom comply or will comply will all applicable United Kingdom regulations and bye-laws governing the emissions resulting from the manufacturing process for 'Seroquel'.

Yours faithfully
For and on behalf of
Zeneca Limited

L Biggins
Assistant Secretary
Zeneca Pharmaceuticals

7.0 FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

No information submitted

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8.0 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

No information submitted

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9.0 USE OF RESOURCES AND ENERGY

No information submitted

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10.0 MITIGATION MEASURES

No information submitted

11.0 ALTERNATIVES TO PROPOSED ACTION

No information submitted

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SECTION 12.

PREPARERS

This assessment was prepared by Martin Rackham, Occupational Hygiene and Environmental Affairs Manager for ZENECA PHARMACEUTICALS. He has a Bachelors Degree in Chemistry and Physiology and a Masters Degree in Occupational Hygiene.

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.

Martin Rackham MSc BSc MIoH
Occupational Hygiene and Environmental Affairs Manager
International Safety, Health and Environment Department
ZENECA Pharmaceuticals

January 1997

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

15.2 Material Safety Data Sheet for ICI 204,636

ZENECA Pharmaceuticals Group

MATERIAL SAFETY DATA SHEET

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Name: ICI 204,636

Address/Phone No. : ZENECA Inc.
Wilmington
Delaware 19897
Phone(24 hr.) Technical : (302) 886-3000
Chemtrec : (800) 424-9300
Medical : (800) 327-8633

Alternative Names
Seroquel

2. COMPOSITION/INFORMATION ON INGREDIENTS

CAS No. : 111974-72-2

HAZARDOUS INGREDIENT(S)	CAS No.
ICI 204,636	111974-72-2

Ingredients not precisely identified are proprietary or nonhazardous.
Values are not product specifications.

3. HAZARDS IDENTIFICATION (as defined by OSHA Hazards Communication Standard, 29 CFR 1910.1200)

A severe irritant to eyes. Risk of serious damage to eyes.
May cause skin irritation in sensitive individuals.
High atmospheric concentrations in excess of the occupational exposure limit may lead to drowsiness
Harmful if swallowed.

Name: ICI 204,636

4. FIRST-AID MEASURES

Inhalation : Remove patient from exposure. Obtain medical attention.
Skin Contact : Remove contaminated clothing. Wash skin with water. If symptoms (irritation or blistering) occur obtain medical attention.
Eye Contact : Immediately irrigate with eyewash solution or clean water, holding the eyelids apart, for at least 10 minutes. Obtain medical attention.
Ingestion : Wash out mouth with water. Obtain immediate medical attention.

Note to Physicians
Symptomatic treatment and supportive therapy as indicated.

5. FIRE-FIGHTING MEASURES

Flash Point (Deg C/Deg F)	: Not applicable.
Flammable Limits	: Not applicable.
Auto Ignition Temperature (Deg C/Deg F)	: No data.
Flammable Powder Class	: A
Minimum Ignition Temperature (Deg C/Deg F)	: 500-550/932-1022
Minimum Ignition Energy (mJ)	: 50-100

Burns with flames.
The material can form flammable dust clouds in air.
Thermal decomposition will evolve flammable vapors.

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

6. ACCIDENTAL RELEASE MEASURES

Moisten spillages with water. Transfer to a container for disposal.
Wash the spillage area with water.

7. HANDLING AND STORAGE

7.1 HANDLING

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

Special Precautions
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.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

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 MSHA-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; full faceshield in addition if splashing is possible.
Other Protective Equipment	: Eyewash station in work area.

Occupational Exposure Limits

HAZARDOUS INGREDIENT(S)	LTEL 8hr TWA ppm	LTEL 8hr TWA mg/m3	STEL ppm	STEL mg/m3	
No ACGIH TLV or OSHA PEL assigned.					
ICI 204,636 Fumarate	-	0.1	-	-	COM

9. PHYSICAL AND CHEMICAL PROPERTIES

Form	: crystalline powder
Color	: white
Melting Point (Deg C)	: 169.5-171.0

Vapor Pressure (mm Hg)	: No data.
Solubility (Water)	: slightly soluble
Partition Coefficient	: <1.10
Specific Gravity	: No data.
Vapor Density (Air= 1)	: No data.

Dissociation constant: 6.6

10. STABILITY AND REACTIVITY

Hazardous Reactions : Stable up to (Deg C) 100

11. TOXICOLOGICAL INFORMATION

Inhalation : No information available. Adverse effects similar to ingestion may occur following exposure to the dust.

Skin Contact : Slight/mild irritant to rat skin. May cause skin irritation in sensitive individuals.
It is not a skin sensitizer.

Eye Contact : Risk of serious damage to eyes.
Severe/very severe irritant to rabbit eyes. Will cause eye irritation in man.

Ingestion : Harmful if swallowed. May produce mild sedation

Long Term Exposure : Chronic ingestion studies in animals have shown that repeated doses produce adverse effects such as cataracts and seizures in dogs.

A study in animals has shown that high doses cause adverse effects on fertility

None of these effects are likely to occur in humans, provided exposure is maintained at or below the occupational exposure limit.

12. ECOLOGICAL INFORMATION

Environmental Fate and Distribution
The substance has no mobility in soil (pH 5.0, 5.8).
The substance has low mobility in soil (pH 7.7).

Persistence and Degradation
Chemical Oxygen Demand (COD) 1.8gO2/g.
Biological Oxygen Demand (BOD 28 DAY) zero
Biodegradability : negligible

Toxicity
LC50 (rainbow trout) (96 hour) (semi-static) 10-100mg/l.
No observed effect concentration (growth rate) (blue green algae) (14 days) 1.0mg/l.
No observed effect concentration (bluegill sunfish) (96 hour) 1.8mg/l.

EC50 (Daphnia magna) (48 hour) 10-100mg/l.
EC50 (green algae) (72 hour) biomass 1-10mg/l.
EC50 (green algae) (72 hour) growth rate 10-100mg/l.
EC50 (bacteria, anaerobic) (15 day(s)) >100mg/l.
EC50 (nitrifying bacteria) (4 hour) >100mg/l.
The substance shows no toxicity to bacteria at the maximum tested concentration of >100mg/l.

No observed effect concentration (cell density) (green algae) (14 days) 2.5mg/l.
No observed effect concentration (growth rate) (green algae) (14 days) 2.5mg/l.

No observed effect concentration (cell density) (blue green algae) (14 days) 4.0mg/l.
No observed effect concentration (growth rate) (blue green algae) (14 days) 32mg/l.

Effect on Effluent Treatment
There is no evidence of inhibition to the aerobic treatment process at a concentration (mg/l) of >100mg/l.

13. DISPOSAL CONSIDERATIONS

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
Empty container retains product residue. Observe all hazard precautions. Do not distribute, make available, furnish or reuse empty container except for storage and shipment of original product. Remove all product residue from container and puncture or otherwise destroy empty container before disposal.

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 the ANSI Standard.

The following sections contain revisions or new statements: 3,11,12,13

MATERIAL SAFETY DATA SHEET

Name: ICI 204,636

GLOSSARY

COH : The company aims to control exposure in its workplace to this limit
TLV : The company aims to control exposure in its workplace to the ACGIH limit
TLV-C: The company aims to control exposure in its workplace to the ACGIH Ceiling 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.