CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-818

ENVIRONMENTAL ASSESSMENT and/or FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

DIOVAN HCT TABLETS

Valsartan / Hydrochlorothiazide Tablets
80/12.5 mg and 160/12.5 mg

NDA 20-818

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-818

DIOVAN HCT TABLETS

[Valsartan / hydrochlorothiazide]

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 Diovan HCT Tablets, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936-1080 prepared an environmental assessment in accordance with 21 CFR 25.31a (a), Tier 0, (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Valsartan and hydrochlorothiazide are synthetic drug substances which are combined in an oral tablet administered for the treatment of hypertension. Valsartan is manufactured by Novartis Pharmaceuticals Corp in Switzerland. Hydrochlorothiazide is purchased from a manufacturer identified in the EA. Combination tablets are manufactured by Novartis Pharmaceuticals Corp in Switzerland. The drug product is packaged by Novartis Pharmaceuticals Corp, Suffern, New York and the facilities of Covance Pharmaceutical Packaging Services (Allentown, PA), Packaging Coordinators (Philadelphia, PA), PACO Pharmaceutical Services (Lakewood, NJ), and Sharp/Ivers-Lee Corp (Conshohocken, PA). All facilities are certified to operate in accord with applicable environmental regulations. The drug product, either 80 mg Valsartan combined with 12.5 mg hydrochlorothiazide or 160 mg Valsartan combined with 12.5 mg hydrochlorothiazide will be used in hospitals, clinics and by patients in their homes.

Valsartan and hydrochlorothiazide and their metabolites will be excreted into the sewer system. Chemical and physical properties indicate that they will be restricted to the aquatic environment. The maximum expected environmental concentrations (MEEC) are well below 1 ppb based on production estimates for each of the five years after approval of the NDA.

Disposal includes out of specification lots, returned, unused or expired product, empty or partly used product and packaging. These will be disposed at licensed incineration facilities and landfills. Empty or partially empty packages generated in American hospitals and clinics will be disposed according to their regulations. Empty or partially empty containers from home use will be disposed in the community solid waste management system which may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed 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.

6/13/97
DATE

PREPARED BY: F Zielinski, Review Chemist
Division of New Drug Chemistry I

6/17/97
DATE

DIVISION CONCURRENCE: Robert Wolters
Division of New Drug Chemistry I

6/30/97
DATE

APPROVED: Nancy B. Sager, Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (Ref.: Vol. 1.8, pages 6 to 20)
Compliance Statements (Ref.: Vol. 1.8, pages 21 to 39)
Material Safety Data Sheets (Ref.: Vol. 1.8)
a) Valsartan (pages 41 to 47)
b) hydrochlorothiazide (pages 48 to 49)

Original: NDA 20-818
HFD-357 FONSI File [NDA 20-818]
HFD-357 Docket File
HFD-205 FOI COPY
HFD-110 Division File
HFD-110 CSO, Kathleen Bongiovanni
HFD-110 Review Chemist, Florian Zielinski

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

DIOVAN HCT TABLETS

Valsartan / Hydrochlorothiazide Tablets
80/12.5 mg and 160/12.5 mg

NDA 20-818

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-818

DIOVAN HCT TABLETS

[Valsartan / hydrochlorothiazide]

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 Diovan HCT Tablets, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936-1080 prepared an environmental assessment in accordance with 21 CFR 25.31a (a), Tier 0, (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Valsartan and hydrochlorothiazide are synthetic drug substances which are combined in an oral tablet administered for the treatment of hypertension. Valsartan is manufactured by Novartis Pharmaceuticals Corp in Switzerland. Hydrochlorothiazide is purchased from a manufacturer identified in the EA. Combination tablets are manufactured by Novartis Pharmaceuticals Corp in Switzerland. The drug product is packaged by Novartis Pharmaceuticals Corp, Suffern, New York and the facilities of Covance Pharmaceutical Packaging Services (Allentown, PA), Packaging Coordinators (Philadelphia, PA), PACO Pharmaceutical Services (Lakewood, NJ), and Sharp/Ivers-Lee Corp (Conshohocken, PA). All facilities are certified to operate in accord with applicable environmental regulations. The drug product, either 80 mg Valsartan combined with 12.5 mg hydrochlorothiazide or 160 mg Valsartan combined with 12.5 mg hydrochlorothiazide will be used in hospitals, clinics and by patients in their homes.

Valsartan and hydrochlorothiazide and their metabolites will be excreted into the sewer system. Chemical and physical properties indicate that they will be restricted to the aquatic environment. The maximum expected environmental concentrations (MEEC) are well below 1 ppb based on production estimates for each of the five years after approval of the NDA.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Environmental Assessment Information

21 CFR 25.31a(a)

Diovan HCT™ Combination Tablets

Valsartan/Hydrochlorothiazide, USP, 80 mg/12.5 mg
Valsartan/Hydrochlorothiazide, USP, 160 mg/12.5 mg

Table of Contents

List of Non-confidential Appendices

Appendix	
Appendix I	Environmental settings description of Novartis overseas facility (Section 4.3.1.)
Appendix II	Environmental settings description of Novartis overseas facility (Section 4.3.1.)
Appendix III	Description and map of environmental settings of Novartis facility - Suffern, New York (Section 4.3.4.)
Appendix IV	Self-certification of compliance for foreign manufacturing facilities (Section 6.4.)
Appendix V	Statement of compliance (Section 6.4.)
Appendix VI	Material Safety Data Sheets (Section 6.5.)
Appendix VII	Curriculum Vitae for preparers (Section 12.)

List of Confidential Appendices

Appendix	
Appendix 1	Valsartan and hydrochlorothiazide, USP Combination tablet NDA Application Technical Summary: Part D: *Chemistry, Manufacturing and Controls Summary*
Appendix 2	Valsartan NDA Application Technical Summary: Part D: *Chemistry, Manufacturing and Controls Summary*
Appendix 3	Esidrix (hydrochlorothiazide, USP) NDA 11-793: S-066 Supplement Summary and Attachment II
Appendix 4	Manufacture of proprietary intermediate for valsartan: •Identification of manufacturer (Section 4.3.1.) •Letter of Authorization for DMF (Section 4.3.1.) •Self-certification of compliance (Section 6.4.)
Appendix 5	•Identification of supplier of hydrochlorothiazide, USP (Section 4.3.2.) •Letter of Authorization for DMF (Section 4.3.2.) •Self-certification of compliance (Section 6.4.)
Appendix 6	Description of environmental settings of contract packaging facilities (Section 4.3.4.)
Appendix 7	Description of environmental settings of waste disposal facilities (Section 4.5.)
Appendix 8	*Ciba monograph: Esidrex/AS, micronized* (Section 5.2.2.)
Appendix 9	•*Ciba monograph: CGP 63170 80 + 12.5 (Valsartan-Hydrochlorothiazide) film-coated tablets* •*Ciba monograph: CGP 63170 160 + 12.5 (Valsartan-Hydrochlorothiazide) film-coated tablets* (Section 5.3.1.)
Appendix 10	*Ciba monograph: Diovan/AS* (Section 5.3.2.)
Appendix 11	•Table I - Fifth year production forecast for valsartan (Section 6.6.) •Table II - Fifth year production forecast for hydrochlorothiazide (Section 6.6.)
Appendix 12	•Table I - Calculation of Expected Introduction Concentration (EIC) for valsartan entering the aquatic environment from patient use (Section 6.6.) •Table II - Calculation of Expected Introduction Concentration (EIC) for hydrochlorothiazide entering the aquatic environment from patient use (Section 6.6.)

Executive summary

The National Environmental Policy Act (NEPA) requires federal agencies to prepare environmental impact statements (EIS) detailing the environmental impact of, and alternatives to, proposals for major federal actions that significantly affect the quality of the human environment. Pursuant to these statutory requirements, procedures for implementation have been issued by the Council on Environmental Quality (CEQ) in 40 CFR Parts 1500-1508.

The Food and Drug Administration (FDA), as a federal agency, has accordingly issued supplemental regulations to implement these requirements in 21 CFR 25.1-50. Section 25.20 states that all actions by the FDA are subject to environmental consideration and must be individually examined for environmental impact unless excluded as a class by categorical exclusion under Section 25.24. This document has been prepared according to the format outlined in 21 CFR 25.31a(a), "Environmental assessment for proposed approvals of FDA-regulated products - Format 1".

Novartis Pharmaceuticals Corporation has filed an NDA for Diovan HCT™ (valsartan and hydrochlorothiazide, USP) combination tablets. Diovan HCT™ combination tablets contain the drug substances valsartan (an effective antihypertensive agent which produces clinically significant reductions in blood pressure that persist over 24 hours when administered once daily) and the thiazide diuretic, hydrochlorothiazide.

An environmental assessment has been prepared for Diovan HCT™ combination tablets, following the format specified. Approval of the NDA for Diovan HCT™ combination tablets will have no impact upon compliance with current emission requirements at any of the overseas manufacturing facilities or at any of the packaging facilities within the United States. It was also concluded from the information provided in this assessment that the maximum anticipated level of valsartan in the environment occurring as a result of the prescription of this drug substance (as Diovan capsules or Diovan HCT™ combination tablets) will be less than 1 part per billion. Similarly, the maximum anticipated level of hydrochlorothiazide in the environment occurring as a result of the prescription of this drug substance (as Esidrix tablets, or in combination with other products, such as Ser-Ap-Es, Apresazide, Lopressor HCT, Lotensin HCT or Diovan HCT™ combination tablets) will be less than 1 part per billion. Thus, this environmental assessment qualifies for a Tier 0 approach, as per CDER *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* (November 1995). Accordingly, format items 7, 8, 9, 10, 11 and 15 have not been included.

Because of the therapeutic benefits associated with the availability and use of Diovan HCT™ Combination Tablets, it is the conclusion of Novartis Pharmaceuticals Corporation that approval is preferable to non-approval, and requests that the FDA issue a **"Finding of No Significant Impact"** for the Diovan HCT™ NDA.

Environmental Assessment Information

An environmental assessment has been prepared in accordance with the requirements stated in 21 CFR Part 25.31a(a) for Diovan HCT™ combination tablets.

1. Date

March 18, 1997 (*original*)

2. Name of applicant

Novartis Pharmaceuticals Corporation

3. Address

59 Route 10
East Hanover, New Jersey 07936-1080

4. Description of the proposed action

4.1. Requested approval

Novartis Pharmaceuticals Corporation has filed a New Drug Application (NDA) for Diovan HCT™ (valsartan and hydrochlorothiazide, USP) combination tablets. Valsartan is a member of a new class of antihypertensive agents which inhibits the renin-angiotensin system by direct blockade of angiotensin II receptors. By contrast, ACE inhibitors block the action of angiotensin I converting enzyme (ACE) and prevent the formation of angiotensin II. However, ACE is also responsible for the degradation of bradykinin, and a blockade of this activity may lead to increased levels of kinin in plasma and tissues. This effect has been implicated in the pathogenesis of both the cough and angioneurotic edema that are side effects of ACE inhibitor therapy. Direct blockade of angiotensin II receptors is considered to be a more specific mechanism of inhibiting the renin-angiotensin system without producing these side effects. Valsartan acts as a potent, selective and competitive antagonist of angiotensin II at the AT_1 receptor subtype.

Hydrochlorothiazide (HCT) is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equal amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone

secretion, increases in urinary plasma loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II; coadministration of an angiotensin II receptor antagonist such as valsartan tends to reverse the potassium loss associated with these diuretics.

Diovan HCT™ is available as tablets for oral administration, containing either 80 mg or 160 mg of valsartan in combination with 12.5 mg hydrochlorothiazide.

For further information regarding the the finished product, Diovan HCT, please refer to the *Chemistry, Manufacturing and Controls Summary* provided for your convenience in Confidential Appendix 1 of this document. This section is identical to documentation found in the overall summary of NDA.

For further information regarding the drug substance valsartan, please refer to the *Chemistry, Manufacturing and Controls Summary* provided for your convenience in Confidential Appendix 2 of this document. This section is identical to documentation found in the overall summary of the original NDA.

For further information regarding the drug substance hydrochlorothiazide, please refer to the information provided in Confidential Appendix 3 of this document. This section is identical to documentation found in Supplement 066 of NDA 11-793.

4.2. Need for action

Approval of this NDA will result in the distribution of Diovan HCT™ combination tablets throughout the United States. Approval will offer patients safe and effective therapy in the treatment of hypertension. Because of the therapeutic benefits associated with the availability and use of valsartan and hydrochlorothiazide, USP to this patient population, approval is justified and preferable to non-approval.

4.3. Sites of production and environmental settings

4.3.1. Manufacture of bulk drug substance: Valsartan

As noted in the *Chemistry, Manufacturing and Controls Summary* (Confidential Appendix 1) of this NDA, the bulk drug substance valsartan is manufactured by:

Novartis Pharmaceuticals Corporation
CH-4002 Basel
Switzerland

Specifically, valsartan drug substance will be chemically manufactured at the following site in Basel, Switzerland:

Novartis
Werke Schweizerhalle
Industriestrasse
CH-4133 Prattein 1, Schweizerhalle
Switzerland

Additionally, valsartan drug substance can be milled at the following site in Basel, Switzerland:

Novartis
Werk Stein
Schaffhauserstrasse
CH-4332 Stein
Switzerland

Descriptions of the environmental settings for these overseas manufacturing facilities are provided in Non-confidential Appendices I and II, respectively.

For technical reasons, an intermediate product is manufactured by a contract manufacturer. This information is classified as confidential business information, and therefore, the identification of this facility and a letter of authorization for its DMF are provided in Confidential Appendix 4.

4.3.2. Manufacture of bulk drug substance: Hydrochlorothiazide

As noted in the *Chemistry, Manufacturing and Controls Summary* (Confidential Appendix 1) of this NDA, the bulk drug substance hydrochlorothiazide, USP is purchased from a supplier. This information is classified as confidential business information, and therefore, the identification of this facility and a letter of authorization for its DMF are provided in Confidential Appendix 5.

Hydrochlorothiazide, USP drug substance is micronized at the following site:

Novartis
Werk Stein
Schaffhauserstrasse
CH-4332 Stein
Switzerland

A description of the environmental settings for this Novartis overseas manufacturing facility is provided in Non-confidential Appendix II.

4.3.3. Manufacture of finished dosage form

As noted in the *Chemistry, Manufacturing and Controls Summary* (Confidential Appendix 1) of this NDA, finished dosage form manufacture occurs at the following facility:

Novartis
Werk Stein
Schaffhauserstrasse
CH-4332 Stein
Switzerland

As previously mentioned, a description of the environmental settings for this facility is provided in Non-confidential Appendix II.

4.3.4. Packaging of finished dosage form

Drug product packaging will occur either at the following Novartis facility:

Novartis Pharmaceuticals Corporation
25 Old Mill Road
Suffern, New York 10901 - 7914

or at the following contract facilities:

An environmental setting description and map for the Novartis facility at Suffern, NY are provided in Non-confidential Appendix III. Descriptions of the environmental settings for the contract packaging facilities are provided in Confidential Appendix 6.

4.4. Sites of product use and environmental settings

Diovan HCT™ combination tablets will be marketed throughout the United States as a solid oral dosage form administered once daily for the reduction of blood pressure. Diovan HCT combination tablets will be available to patients through prescription only.

4.5. Sites of product disposal and environmental settings

Novartis Pharmaceutical Corporation publishes a report entitled *"Hazardous & Chemical Waste Disposal Sites"*. All hazardous waste disposal facilities listed in this report are recommended for approval by Novartis Pharmaceutical Corporation only after Novartis personnel complete and submit an inspection and audit report. A list of non-hazardous disposal facilities is also provided, and it is the Corporation's recommendation that these facilities be audited periodically.

All waste generated by the packaging of Diovan HCT™ combination tablets, as well as all returned or rejected production material, is classified as non hazardous waste. Solid process residuals (returned or rejected production material, laboratory waste) will be shipped from

Novartis for off-site incineration at permitted incineration facilities. The incineration facilities currently used by Novartis and descriptions of the environmental settings are provided in Confidential Appendix 7. These non-hazardous waste disposal facilities are listed in the current Novartis Pharmaceutical Corporation *"Hazardous & Chemical Waste Disposal Sites"* report.

5. Identification of chemical substances that are the subject of the proposed action

5.1. Drug product

Trade name: Diovan HCT™ combination tablet

Common name: Valsartan - Hydrochlorothiazide combination tablet

Other names: CGP 63170

5.2. Drug substances

5.2.1. Valsartan

Common name: Valsartan

Chemical name: (N)-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,,1'-biphenyl]-4-yl]methyl]-L-Valine

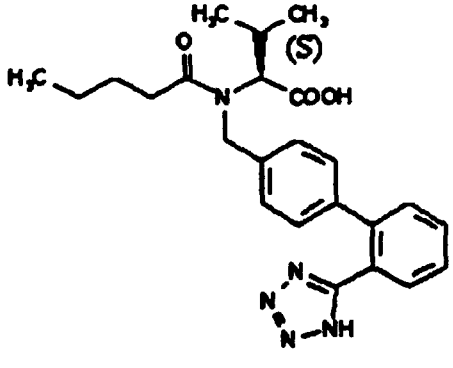
Other names: CGP 48933; Diovan

CAS number: 137682-53-4

Molecular formula: $C_{24}H_{29}N_5O_3$

Molecular weight: 435.5

Structural formula:



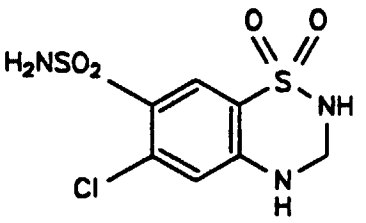
Description:

Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

For further information on the physical and chemical properties of the drug substance Valsartan, please refer to the *Chemistry, Manufacturing and Controls Summary* (Confidential Appendix 2). This document is identical to that provided in the original NDA 20-665 for Valsartan.

5.2.2. Hydrochlorothiazide

Common name:	Hydrochlorothiazide, USP
Chemical name:	6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide
Other names:	Esidrix®; Esidrex; HCT; HCTZ
CAS number:	137682-53-4
Molecular formula:	$C_7H_8ClN_3O_4S_2$
Molecular weight:	297.73
Structural formula:	



Description:

Hydrochlorothiazide, USP is a white, or practically white, practically odorless crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide (DMF); sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids.

For further information on the physical and chemical properties of the drug substance hydrochlorothiazide, USP, please refer to the information provided in *Ciba monograph: Esidrex/AS, micronized* (Confidential Appendix 8).

5.3. Impurities

5.3.1. Drug Product

Manufacture of the drug product, Diovan HCT is controlled for the amount of the D-enantiomer of valsartan as well as other related substances. Please refer to *Ciba monograph: CGP 63170 80 + 12.5 (Valsartan-Hydrochlorothiazide) film-coated tablets* and *Ciba monograph: CGP 63170 160 + 12.5 (Valsartan-Hydrochlorothiazide) film-coated tablets* (Confidential Appendix 9) for information on the identification and concentration of the impurities which may be present in the drug substance valsartan.

5.3.2. Drug Substances

Manufacture of the drug substance, valsartan is controlled so that the total amount of the D-enantiomer of valsartan does not exceed 1.5%, and the total amount of other related substances (excluding the D-enantiomer) does not exceed 0.5%. Please refer to *Ciba monograph: Diovan/AS* (Confidential Appendix 10) for information on the identification and concentration of the impurities which may be present in the drug substance valsartan.

Manufacture of the drug substance, hydrochlorothiazide, is controlled so that the total amount of other related substances does not exceed 0.5% (in each case), and the total amount of related substances is not more than 1.0%. Please refer to *Ciba monograph: Esidrex/AS, micronized* (Confidential Appendix 8) for further information on the identification and concentration of other related substances which may be present in the drug substance hydrochlorothiazide, USP.

6. Introduction of substances into the environment

6.1. Sites of production

6.1.1. Manufacture of bulk drug substance: Valsartan

Valsartan drug substance will be chemically manufactured at the following site in Basel, Switzerland:

Novartis
Werke Schweizerhalle
Industriestrasse
CH-4133 Prattein 1, Schweizerhalle
Switzerland

Additionally, Valsartan drug substance can be milled at the following site in Basel, Switzerland:

Novartis
Werk Stein
Schaffhauserstrasse
CH-4332 Stein
Switzerland

For technical reasons, one of the intermediate products is manufactured by a contract manufacturer. The identity of this contract manufacturer is considered classified confidential business information.

6.1.2. Manufacture of bulk drug substance: Hydrochlorothiazide

The bulk drug substance hydrochlorothiazide, USP is supplied by a manufacturer. The identity of this supplier is considered classified confidential business information.

Hydrochlorothiazide, USP drug substance is purchased from this supplier and is then micronized at the following site:

Novartis
Werk Stein
Schaffhauserstrasse
CH-4332 Stein
Switzerland

6.1.3. Manufacture of finished dosage form

The finished dosage form, Diovan HCT 80 mg / 12.5 mg and 160 mg / 12.5 mg combination tablets, will be manufactured at the following facility:

Novartis
Werk Stein
Schaffhauserstrasse
CH-4332 Stein
Switzerland

Information on the manufacture of Diovan HCT combination tablets and its composition are contained in Attachments of the Diovan HCT combination tablets *Chemistry, Manufacturing and Controls Summary* (Confidential Appendix 1).

6.1.4. Packaging of finished dosage form

Packaging operations will take place at the Novartis facility in Suffern, NY or at the following contract packaging facilities:

6.2. Substances expected to be emitted and controls exercised

6.2.1. Air emissions and controls

Novartis - Suffern, New York

The only air emissions associated with the packaging of Diovan HCT™ (valsartan and hydrochlorothiazide, USP) combination tablets are particulates and volatile organic compounds (VOCs). The total amount of particulate emissions generated during the packaging of Diovan HCT combination tablets will be trace, having been controlled by dust collectors with a 99.9% capture efficiency for incoming particulates. (Currently, the Suffern facility is permitted to emit up to 9 lb. of particulates annually.)

Insignificant quantities of VOCs are generated during the cleaning of the packaging lines and through printing. Packaging lines are cleaned with isopropyl alcohol. Cleaning operations

generate fugitive VOCs, while the emissions for printing operations are sent to a carbon bed. Since the site's total annual permitted VOC emission is below the New York State significant source threshold (25 tons), Suffern is classified as a minor source (not a Title V facility). With average annual VOC emissions of approximately 10 tons, Suffern will continue to be in compliance with EPA and NYSDEC regulations, even with the additional VOC emissions associated with the packaging operations for Diovan HCT combination tablets.

The emissions of particulates and VOCs for the packaging of Diovan HCT combination tablets during the forecasted peak production year (see section 6.6. and Confidential Appendix 11) will be in compliance with the Suffern facility's permitted emission levels.

6.2.2. Waste water discharges and controls

Novartis - Suffern, New York

Process and domestic waste water is conveyed from the facility via a gravity sewerage system to an on-site sewerage pumping station. This flow is then directed to the Village of Suffern publicly-owned treatment works (POTW). The Village system is designed to process 1.8 million gallons per day (MGD). The average flow from the facility is approximately 144,600 gallons per day (GPD). The POTW regulates the Suffern facility for its discharge through a state-authorized pre treatment permit program. This program regulates the facility for flow, pH, biochemical oxygen demand (BOD), total suspended solids (TSS), oil, grease, copper, zinc, mercury, cyanide, toluene and methylene chloride. Reporting is submitted on a semi-annual basis.

6.2.3. Solid waste and controls

Novartis - Suffern, New York

All rejected production material from the packaging of Diovan HCT™ combination tablets is sent off-site for incineration at facilities which must operate in conformance with permits issued under the authority of the applicable Federal, state and local regulations. All facilities utilized for the disposal of solid process residuals are inspected periodically by Novartis personnel to ensure conformance with Federal and state regulations. All packaging components which can be recycled will be sold.

Returned goods

Products returned to Novartis Pharmaceuticals Corporation by the customer are evaluated by the Quality Control Department. Those materials which must be discarded are tested and evaluated so as to properly classify them. Those that must be managed in accordance with applicable Federal, state and local regulations are appropriately managed and shipped off-site to disposal facilities as described in section 4.5. [Sites of product disposal and environmental settings]. Incineration is the method of choice for destruction of wastes.

Contract packaging facilities

Contract packaging facilities dispose of non hazardous solid waste (i.e., product packaging materials) generated at their facilities through disposal facilities permitted for non hazardous waste.

Incineration facilities

Only incineration facilities approved by Novartis are used for the disposal of returned or rejected products as well as wastes generated during product packaging. The incineration of returned and rejected materials generates residual solids, which are disposed of by the individual disposal sites in accordance with their operating permits in permitted landfills. Expected air emission from pollution control equipment associated with the incineration of packaging wastes are water vapor, carbon monoxide, carbon dioxide and small quantities of nitrous oxides. The incineration of discarded packaging materials will also generate waste water. This water is treated by the incineration facility before discharge in accordance with the operating permits issued by the state in which the facility is located. Whenever possible, discarded packaging components are sold to a reclaimer/recycler.

6.3. Citation of compliance with applicable emission requirements

6.3.1. Citations for air emissions

Novartis - Suffern, New York

Air emissions must be in compliance with the Clean Air Act. In the State of New York, air emissions are regulated under Title 6 of the New York State Codes, Rules and Regulations (*NYCRR*). The Suffern facility is covered by the following Parts for packaging and printing operations: *200*, General Provisions; *201*, Permits and Registrations; *212*, Existing Sources; *227*, Stationary Combustion Sources; *228*, Surface Coating; *233*, Pharmaceutical Manufacturing Processes; *234*, Graphic Arts.

6.3.2. Citations for waste water

Novartis - Suffern, New York

Aqueous emissions must be in compliance with the Clean Water Act. New York is authorized by the Federal government to regulate these emissions under *6 NYCRR*. The Suffern facility discharges waste water to the Village of Suffern POTW under a permit issued by the Village of Suffern. The POTW, in turn, operates under a State Pollutant Discharge Elimination System (SPDES) permit issued by the State of New York under Title NYCRR.

Contract packaging facilities

Contract packaging facilities dispose of non hazardous solid waste (i.e., product packaging materials) generated at their facilities through disposal facilities permitted for non hazardous waste.

Incineration facilities

Only incineration facilities approved by Novartis are used for the disposal of returned or rejected products as well as wastes generated during product packaging. The incineration of returned and rejected materials generates residual solids, which are disposed of by the individual disposal sites in accordance with their operating permits in permitted landfills. Expected air emission from pollution control equipment associated with the incineration of packaging wastes are water vapor, carbon monoxide, carbon dioxide and small quantities of nitrous oxides. The incineration of discarded packaging materials will also generate waste water. This water is treated by the incineration facility before discharge in accordance with the operating permits issued by the state in which the facility is located. Whenever possible, discarded packaging components are sold to a reclaimer/recycler.

6.3. Citation of compliance with applicable emission requirements

6.3.1. Citations for air emissions

Novartis - Suffern, New York

Air emissions must be in compliance with the Clean Air Act. In the State of New York, air emissions are regulated under Title 6 of the New York State Codes, Rules and Regulations (*NYCRR*). The Suffern facility is covered by the following Parts for packaging and printing operations: *200*, General Provisions; *201*, Permits and Registrations; *212*, Existing Sources; *227*, Stationary Combustion Sources; *228*, Surface Coating; *233*, Pharmaceutical Manufacturing Processes; *234*, Graphic Arts.

6.3.2. Citations for waste water

Novartis - Suffern, New York

Aqueous emissions must be in compliance with the Clean Water Act. New York is authorized by the Federal government to regulate these emissions under *6 NYCRR*. The Suffern facility discharges waste water to the Village of Suffern POTW under a permit issued by the Village of Suffern. The POTW, in turn, operates under a State Pollutant Discharge Elimination System (SPDES) permit issued by the State of New York under Title NYCRR.

6.3.3. Citations for solid waste

Novartis - Suffern, New York

All solid wastes must be disposed of in accordance with the applicable regulations included in NYCRR. Since all solid wastes are sent off-site for disposal, this requires the use of licensed transporters and permitted disposal facilities.

Contract packaging facilities

Contract packaging facilities must conform to all applicable Federal, state and local regulations, and must manage waste materials according to Novartis standards. All solid wastes generated by the contract packaging facilities listed in Section 4.3.4. are sent only to permitted incineration facilities. Non hazardous solid waste may be returned by the contract packager to Novartis for disposal, or directly routed to one of the disposal facilities as described in Section 4.5. All disposal facilities on Novartis' approved list utilize incineration as the method of treatment.

6.4. Certification of compliance

An environmental protection certificate has been obtained from the Canton of Basel-Landschaft for the chemical production of valsartan active substance at the Novartis Werke Schweizerhalle facility. A copy of this certificate is provided in Non-confidential Appendix IV.

A self-certification of compliance for the milling of valsartan active substance and the manufacture of Diovan HCT combination tablets at the Novartis Werk Stein facility is provided in Non-confidential Appendix IV.

A self-certification of compliance for the purification and micronization of hydrochlorothiazide, USP at the Novartis Werk Stein facility is provided in Non-confidential Appendix IV.

A self-certification of compliance with respect to environmental and safety laws and regulations from the contract manufacturer of an intermediate product for valsartan active substance is provided in Confidential Appendix 4, as this information has been classified as confidential business information.

A self-certification of compliance with respect to environmental and safety laws and regulations from the manufacturer of hydrochlorothiazide active substance is provided in Confidential Appendix 5, as this information has been classified as confidential business information.

A signed statement of compliance by Novartis Pharmaceuticals Corporation regarding environmental permits required for the packaging of Diovan HCT™ Combination Tablets at its facility in Suffern, New York is provided in Non-confidential Appendix V.

6.5. Compliance with OSHA Hazard Communication Standard

In accordance with the requirements of the Occupational Health and Safety Administration (OSHA) Hazard Communication Standard, 29 CFR 1910.1200, Novartis Pharmaceuticals Corporation has established a Hazard Communication/Right-to-Know program at the Suffern, New York site which covers all employees. Under this program, all chemicals are first evaluated to determine whether they meet the OSHA criteria for hazardous chemicals. All containers are then labeled with the chemical name, CAS number, and information regarding the nature of hazards associated with that substance. Material Safety Data Sheets (MSDSs) are available for all chemicals handled at the plant, with MSDSs prepared internally for those materials used in the production of finished dosage forms. These are available in each area where the substance is used, as well as in a central location. The program also provides the required employee training, which includes hazard recognition, interpretation of information on MSDSs and labels, the safe handling of selected classes of hazardous materials, and proper use of personal protective equipment.

To demonstrate compliance with the Federal and state occupational health requirements, an MSDS for each drug substance is included in Non-confidential Appendix VI.

6.6. Quantities and concentrations expected to enter the environment

The concentration of valsartan expected to be released into the environment as a result of prescription of the approved drug product Diovan capsules as well as Diovan HCT™ combination tablets (the subject of the current NDA) for the treatment of hypertension was determined based upon market research. The marketing forecast for valsartan during the peak production year is provided in Table I of Confidential Appendix 11.

The concentration of hydrochlorothiazide expected to be released into the environment as a result of prescription of the approved drug products Esidrix tablets, Ser-Ap-Es, Apresazide, Lopressor HCT, Lotensin HCT as well as Diovan HCT™ combination tablets (the subject of the current NDA) was determined based upon market research. The marketing forecast for hydrochlorothiazide during the peak production year is provided in Table II of Confidential Appendix 11.

An Expected Introduction Concentration (EIC) has been calculated for the drug substance valsartan. This EIC is based upon the forecasted peak year of maximum sales. The EIC value for valsartan, the supporting calculations and the assumptions made for this calculation are provided in Table I of Confidential Appendix 12.

An Expected Introduction Concentration (EIC) has been calculated for the drug substance hydrochlorothiazide. This EIC is based upon the forecasted peak year of maximum sales. The EIC value for hydrochlorothiazide, the supporting calculations and the assumptions made for this calculation are provided in Table II of Confidential Appendix 12.

It was concluded from the information provided in this Appendix that the maximum anticipated levels of valsartan and hydrochlorothiazide in the environment occurring as a result of this

indication would be significantly less than 1 part per billion Accordingly, format items 7, 8, 9, 10, 11 and 15 have not been included for either drug substance[1].

12. List of preparers

A curriculum vitae, documenting the qualifications and credentials for each of the contributors to this environmental assessment, is provided in Non-confidential Appendix VII.

13. Certification

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm responsible for preparation of the environmental assessment.
The undersigned official certifies that the EA summary document (pages 1 - 20) and Appendices I - VII (pages 21 - 54) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6.

Joyce Ann Sinno, Ph.D. 18 March 97

Joyce Ann Sinno, Ph.D. Date
Manager, Drug Regulatory Affairs - CMC

14. References

1. Center for Drug Evaluation and Research (CDER), November 1995. *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements.*

Appendices

Non - Confidential

Diovan HCT™
Combination Tablets

Environmental Assessment Information

Appendix I

Appendix I

Description of environmental settings: Novartis overseas facility - Schweizerhalle, Switzerland (Section 4.3.1.)

Novartis
Werke Schweizerhalle
CH-4133 Prattein 1, Schweizerhalle
Switzerland

This Novartis Pharmaceutical Chemical production facility is located within the "Novartis Werke Schweizerhalle AG" site. This site is situated in the industrialized zone of Schweizerhalle, approximately five miles east of the City of Basle, adjacent to the Rhine River which is also the boundary to the Federal Republic of Germany. Novartis Werke Schweizerhalle occupies an area of approximately 52 acres. Approximately 2,250 people are employed at the site. The surrounding neighborhood consists mainly of chemical industry.

Air Resources

Air quality in this area is in compliance with cantonal and federal standards set for sulfur oxides, nitrous oxides and ozone.

Water Resources

Potable water is supplied by the public Hardwasser AG. Non-potable water is drawn from wells within the works (Rhine water). The waste water streams stemming from chemical production are separated into "polluted" and "non-polluted" (cooling water) waste water. The "non-polluted" water is discharged directly into the Rhine River. The "polluted" water, after an on-site pretreatment (if necessary), as well as sanitary waste water and storm water drainage goes to the "ARA Rhein"- a sewage treatment plant jointly used by the public and the industry. This is finally discharged into the Rhine River.

Land Resources

The Schweizerhalle site, a level terrain, lies over essentially sedimentary type formations. It is fully developed, being covered by buildings, roadways and railroads.

6.2. Controls in Effect

Air Controls

Air emissions stemming from the synthesis of bulk drug substances are controlled by equipment such as surface condensers, brine-cooled vent condensers (- 15°C) and scrubber

systems operating with either plain water or acidic, basic or oxidizing aqueous solutions. Air emissions from the on-site incinerator are controlled by a series of scrubbers operating with aqueous absorption mediums. The equipment is in compliance with permits of the Department of Commerse, Industry and Employment of the Canton of Basel-Landschaft (= Amt fuer Gewerbe, Handel und Industrie des Kantons Basel-Landschaft) and the Department of Air Pollution Control (= Lufthygieneamt).

Liquid Controls

All waste solvents are burned in an on-site incinerator. All process waste water goes, if necessary after on-site pretreatment, to the "ARA Rhein", a public-owned Joint Waste Water Treatment Plant. The effluent of this plant is discharged into the Rhine River. This procedure is in compliance with the permit issued by the Department of Commerce, Industry and Employment of the Canton of Basel-Landschaft (= Amt fuer Gewerbe, Handel und Industrie des Kantons Basel-Landschaft) and the Water Protection Agency (= Kantonales Gewaesserschutzamt).

Solids Controls

All solid process residuals (like dusts, filter residues or rejected production material) are sent to the rotary kiln, working at approximately 1200°C owned by Novartis at its Basle site.

6.3. Citations

All Novartis facilities in Switzerland must be in compliance with the following regulations issued by the Swiss Federal Government:

Air Citations

Federal Air Pollution Control Regulation = "Luftreinhalteverordnung" (LRV) 814.318.142.1 (12/16/85, latest edition 1/1/87).

Water Citations

Federal Regulation to Introduce Waste Waters into Rivers and Lakes = "Verordnung ueber Abwassereinleitungen" 814.225.21 (12/8/75, latest edition 4/1/87).

Solid Waste Citations

Federal Regulation for the Transport and Disposal of Special Waste = "Verordnung ueber den Verkehr mit Sonderabfaellen," 814.014 (11/12/86 latest edition, 1/10/89).

Non - Confidential

Diovan HCT™
Combination Tablets

Environmental Assessment Information

Appendix II

Appendix II

Description of environmental settings: Novartis overseas facility - Stein, Switzerland (Section 4.3.1.)

Novartis
Werk Stein
Schaffhauserstrasse
CH-4332 Stein, Switzerland

The Novartis Stein Works is comprised of pharmaceutical production units, the Pharmaceutical Chemical Production milling plant, and facilities for pharmaceutical and agricultural research. The Stein site is situated on 135 acres. Only a minor portion of the site is developed, being covered with buildings, roadways, parking lots and landscaped areas. The remainder of the property is farmland. Approximately 1,200 people are employed by the Stein works.

The site is located in the Canton of Aargau, Switzerland, adjacent to the Rhine River. It is located approximately 20 miles east of the City of Basle (Switzerland). The surrounding area is primarily farmland. The Village of Stein (Switzerland) and, across the Rhine River, the resort town of Bad Saeckingen (Germany) are in close proximity to the facility. The climate of this area is temperate.

Terrain

The Stein site is located upon level terrain and lies over essentially sedimentary type formations.

Air resources

Air quality in this area is in compliance with cantonal and federal standards set for sulfur oxides, nitrous oxides and ozone.

Water resources

Potable water is obtained from the Village of Stein water supply, originating from wells located close to the Stein site. Cooling water, originating from wells on the site, is of the same quality as the public water supply. Cooling water and storm water drainage are discharged into the Rhine River. Production waste water and sanitary water are discharged to the Joint Sewage Treatment Plant of Stein and Bad Saeckingen; which ultimately discharges into the Rhine River.

6.2. Controls in effect

Air controls

Air emissions from drying and milling operations relevant to this product are controlled by equipment such as filter type dust collectors. A house vacuum is used to control dust created by process equipment, clean up minor spills and clean equipment between operations. All emission points are operated to comply with permits issued by the Department of Industry and Commerce of the Canton of Aargau (= Industrie- und Gewerbeamt des Kantons Aargau).

Liquid controls

All waste solvents are sent to the incinerator owned by Novartis at the Schweizerhalle site. The waste water is discharged for purification to the Sewage Treatment Plant of the City of Bad Saeckingen (Federal Republic of Germany) and is in compliance with permits issued by the Department of Water production of the Canton of Aargau (=Abteilung Gewaesser des Kantons Aargau) and the Joint Association for Sewage Water Treatment of the Cities of Stein and Bad Saeckingen (= Abwasserverband Stein-Bad Saeckingen).

Solids controls

All solid process residuals (like filter residues or rejected production materials) are sent to the rotary kiln, working at approximately 1200°C, owned by Novartis at the Schweizerhalle site. All packaging components that can be recycled are sold to Klein Company, Hornussen (Aargau), Switzerland, for that purpose. Aluminum containing tablet packaging components are separated out and sent to Refonda Co., Niederglatt (Zuerich), Switzerland, for recycling.

6.3. Citations of compliance with applicable emission requirements

All the Novartis facilities in Switzerland must be in compliance with the following regulations issued by the Swiss Federal Government:

Citations for air

Federal Air Pollution Control Regulation = "Luftreinhalteverordnung" (LRV) 814.318.142.1 (12/16/85, latest edition 1/1/87).

Citations for waste water

Federal Regulation to Introduce Waste Waters into Rivers and Lakes = "Verordnung ueber Abwassereinleitungen" 814.225.21 (12/8/75, latest edition 4/1/87).

Citations for solid waste

Federal Regulation for the Transport and Disposal of Special Waste = "Verordnung ueber den Verkehr mit Sonderabfaellen," 814.014 (11/12/86 latest edition, 1/10/89).

Non - Confidential

Diovan HCT™
Combination Tablets

Environmental Assessment Information

Appendix III

Appendix III

Description and map of environmental settings of Novartis facility: Suffern, NY
(Section 4.3.3.)

Novartis Pharmaceuticals Corporation
25 Old Mill Road
Suffern, New York 10901-7914

This Novartis pharmaceutical manufacturing facility is located in the Villages of Suffern and Montebello, Rockland County, New York (combined population 14,950) on 162 acres, approximately 30 miles northwest of New York City. The manufacturing facility, which resides within the boundaries of the Village of Suffern, consists of two main buildings, a new docking facility, an automated warehouse structure and several auxiliary buildings with a combined total floor space of approximately 454,000 square feet. The site is bounded by the New York State Thruway on the north, Hemion Road on the east, the Conrail Piermont Line on the south and the Plaza Material Corp. quarry on the west. Wooded ridges on its east and west sides border a flat valley where the facility, parking area and landscaped area lie. The site employs an average workforce of approximately 611 people. The surrounding neighborhood includes retail businesses, light industry and private residences. The topography of the region is varied. The climate is temperate, with an average annual rainfall of 43.5 inches. A map of the facility follows.

Terrain - The developed portion of the site, approximately 33 acres, is generally flat, with an average elevation of approximately 320 feet above sea level. The nature of the soil is characterized as glacial deposits, consisting of sand, gravel and a till mixture of sand, gravel, boulders and clay, with sandstone and shale bedrock.

Water Resources - The Suffern facility is located in a drainage basin with a total of 295 acres. During storm events, stormwater runoff from this basin is channeled naturally through the Novartis's property, eventually discharging through a culvert under Route 287, to Lake Antrim, which eventually feeds into the Mahwah River. Stormwater runoff from the facility is directed to this system through a standard gravity-flow conduit system designed specifically for stormwater runoff conveyance. Four (4) distinct wetland areas have been delineated at the site, totaling 18.6 acres. None of these areas fall under the NY State Department of Environmental Conservation (NYSDEC) regulations governing wetlands protection (12.4 acres or greater). However, three of these four wetlands areas do fall under both Federal Clean Water Act (CWA) regulations and the US Army Corps of Engineer Environmental Protection Regulations.

Process and domestic wastewater are conveyed from the facility via a gravity sewerage system to an on-site sewerage pumping station. This flow is then directed to the Village of Suffern publicly owned treatment works (POTW) at an average flowrate of 144,600 gallons per day (GPD). This POTW is designed to process 1.8 million gallons per day (MGD). The POTW regulates the Suffern facility for its discharge through a Federally-authorized pretreatment permit program. This program regulates the facility for flow, pH, biochemical oxygen demand (BOD), total suspended solids (TSS), oil, grease, copper, zinc, mercury, cyanide, toluene and methylene chloride. Reporting is submitted on a semi-annual basis. All domestic and fire protection water is purchased from the Village of Suffern, which operates a well field, and is interconnected with the Spring Valley Water Company for supplemental purposes.

Air Quality - Suffern is part of the air quality geographical area regulated under the New York - New Jersey - Connecticut Interstate Air Quality Control Region of the Environmental Protection Agency (EPA). Locally, Suffern air quality is regulated by both the NYSDEC and the Rockland County Department of Health. Enforcement issues are handled jointly.

Regional air quality designations are given in Part 81 of the 40 Code of Federal Regulations (CFR). Suffern is currently in compliance with the National Ambient Air Quality Standards (NAAQS) for particulate matter, nitrogen dioxide, sulfur oxides and carbon monoxide. However, Suffern, along with the entire State of New York, is in non-compliance with the NAAQS for ozone.

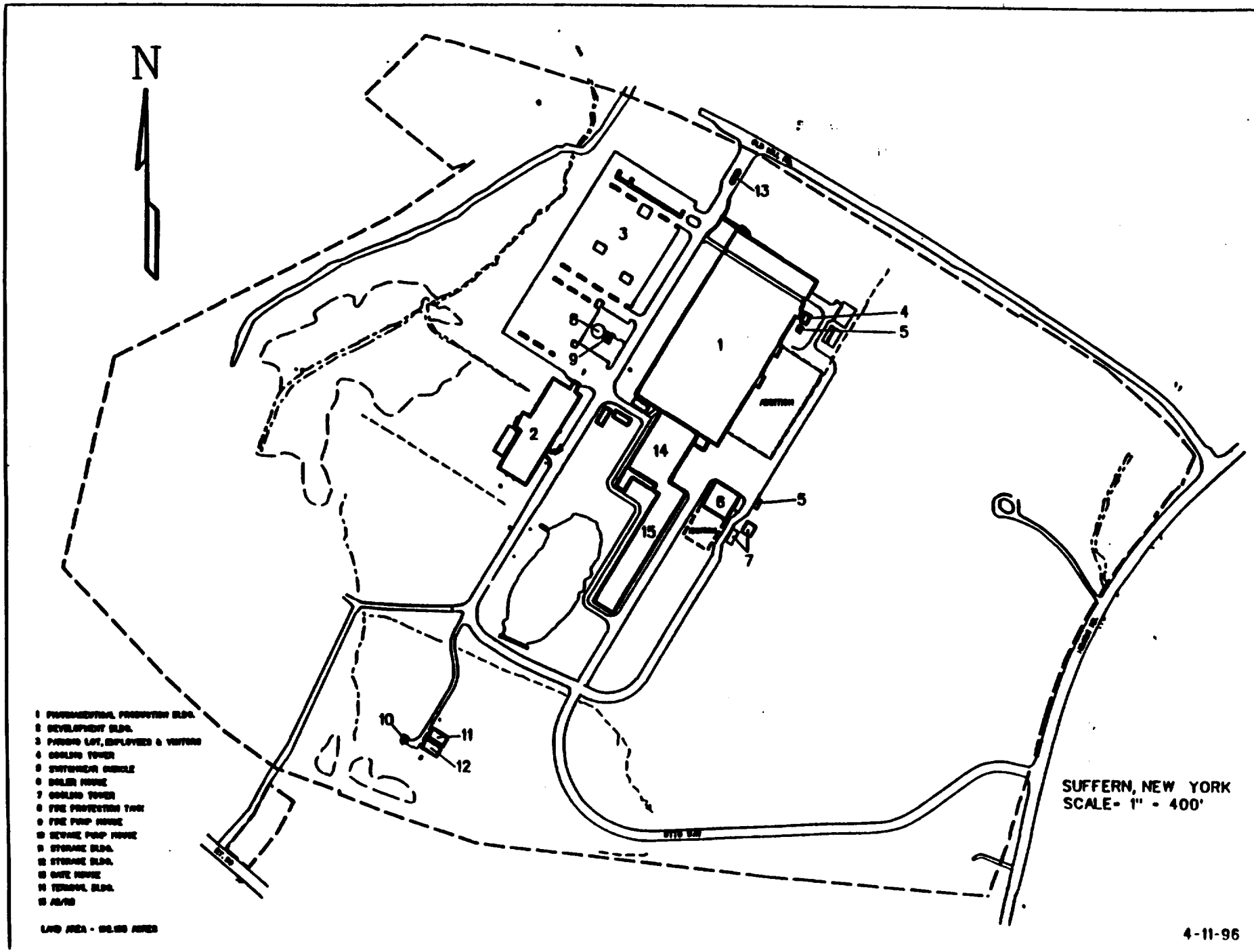
Emissions of regulated substances into the air are reported to Federal, state and local authorities under Title III of the Superfund Amendments and Reauthorization Act of 1986 (SARA). SARA Title III requires affected facilities to track and submit emission inventories annually. Novartis Corporation has been meeting the requirements of SARA Title III since the inception of the program in 1987 and will continue to comply. New York is required to submit to the EPA a State Implementation Plan (SIP) detailing how New York meets all Federal air quality requirements. Novartis fully complies with the SIP outlined by New York. The Clean Air Act Amendments of 1990 promulgated many new air regulations. New York is currently revising their SIP to reflect these new regulations. Novartis intends to fully comply with the new SIP.

In the State of New York, air emissions are regulated under Title 6 of the New York State Codes, Rules and Regulation (NYCRR). As required by these regulations, Novartis maintains an active air permit program. All permits have been, and will continue to be, renewed and updated as process/facility changes occur. New permits will be obtained as required. Where appropriate, Novartis has installed state-of-the-art pollution controls to minimize air emissions. In addition, stack tests have been, and will continue to be, performed for all relevant emission points to ensure compliance.

In the County of Rockland, air emissions are regulated under Article XII of the Sanitary Code of the County of Rockland. As required by County regulations, Novartis maintains an active air permit program. All permits have been, and will continue to be, renewed and updated as changes occur.

Map

Suffern, New York


N
SUFFERN, NEW YORK
SCALE- 1" - 400'
4-11-96

Non - Confidential

Diovan HCT™
Combination Tablets

Environmental Assessment Information

Appendix IV

4410 Liestal, Rheinstrasse 29
Telefon 061 925 51 11
Telefax 061 925 69 46

Bau- und Umweltschutzdirektion
Kanton Basel-Landschaft

Liestal

Liestal, den 18. Dezember 1995

Umweltschutzbescheinigung

(Gültig bis 31. Dezember 1997)

Environmental protection certification

(Valid until 1997-12-31)

Die Bau- und Umweltschutzdirektion bestätigt, dass die Firma

CIBA-GEIGY
WERKE SCHWEIZERHALLE AG
POSTFACH 1130, CH-4133 PRATTELN

über sämtliche Bewilligungen verfügt, die aufgrund der eidgenössischen und kantonalen Umweltschutzgesetzgebung für ihren Betrieb zur Herstellung von Valsartan nötig sind. Im weiteren kann bestätigt werden, dass bei regelmässigen Kontrollen, welche die kantonalen Behörden im Betrieb 2060 durchführen, bis jetzt keine nennenswerten Verstösse gegen die Umweltschutzgesetzgebung festgestellt worden sind.

The department for construction and environmental protection confirms that the company

CIBA-GEIGY
WERKE SCHWEIZERHALLE AG
POSTFACH 1130, CH-4133 PRATTELN

has all the permits required by both federal and cantonal swiss environmental protection laws and regulations to operate a plant for the production of Valsartan. This document furthermore confirms that regular inspections of the 2060 plant by local authorities up to now have never shown any noteworthy infringements against environmental protection regulations.

Die Bau- und Umweltschutzdirektion ist im Kanton Basel-Landschaft für den Vollzug aller relevanten Gesetze und Verordnungen des eidgenössischen und kantonalen Umweltrechts zuständig.

The department for construction and environmental protection is the authority that is competent on the territory of the canton of Basel-Land to enforce the relevant federal and cantonal laws and regulations on the protection of the environment.

Die Vorsteherin der Bau- und Umweltschutzdirektion
The Minister for Construction and Environmental Protection

Elsbeth Schneider-Kenel

NOVARTIS

Dr. Gerd Schwalbach
Head of Safety and
Environmental Protection
Service

Novartis Pharma AG
Site Stein
WST-107.1.15
CH-4332 Stein/AG

Tel 0041-62-868 6327
Fax 0041-62-868 6846

Self Certification of Compliance with respect to Environmental and Safety Laws and Regulations

1. The Company NOVARTIS operates facilities for chemical and pharmaceutical manufacturing at the following address:

   NOVARTIS Pharma AG Site Stein
   Postfach
   CH-4332 STEIN

2. These production facilities may only operate in accordance with permits issued by the responsible Authorities. In the permit are laid down the purpose for which buildings and plants may be used and the legal conditions with which the Company must comply.

3. The above-described certification also covers the milling of

   DIOVAN (Valsartan)

   and the preparation of pharmaceutical products containing

   DIOVAN HCT

4. All buildings and plants of NOVARTIS must comply with the federal and contonal laws and regulations concerning safety, protection of the environment, and working conditions.

5. The relevant departments of the Cantonal Authorities perform inspections.

6. Any subsequent increase in production at the above named facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

7. On the basis of the inspection performed, it can be confirmed that there exists no indication of violation of the applicable laws and regulations.

J. Schwalbach

Dr.Gerd Schwalbach

NOVARTIS

Dr. Gerd Schwalbach
Head of Safety and
Environmental Protection
Service

Novartis Pharma AG
Site Stein
WST-107.1.15
CH-4332 Stein/AG

Tel 0041-62-868 6327
Fax 0041-62-868 6846

Self Certification of Compliance with respect to Environmental and Safety Laws and Regulations

1. The Company NOVARTIS operates facilities for chemical and pharmaceutical manufacturing at the following address:

   NOVARTIS Pharma AG Site Stein
   Postfach
   CH-4332 STEIN

2. These production facilities may only operate in accordance with permits issued by the responsible Authorities. In the permit are laid down the purpose for which buildings and plants may be used and the legal conditions with which the Company must comply.

3. The above-described certification also covers the milling of

   Hydrochlorthiazide (ESIDREX)

4. All buildings and plants of NOVARTIS must comply with the federal and cantonal laws and regulations concerning safety, protection of the environment, and working conditions.

5. The relevant departments of the Cantonal Authorities perform inspections.

6. Any subsequent increase in production at the above named facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

7. On the basis of the inspection performed, it can be confirmed that there exists no indication of violation of the applicable laws and regulations.

Dr. Gerd Schwalbach

Non - Confidential

Diovan HCT™
Combination Tablets

Environmental Assessment Information

Appendix V

Novartis Pharmaceuticals Corporation
556 Morris Avenue
Summit, NJ 07901-1398

Tel 201 503 8300

NOVARTIS

Statement of Compliance

Novartis Pharmaceuticals Corporation states that, to the best of its knowledge, it is in compliance with, or on a schedule to be in compliance with, all requirements set forth in all applicable Federal, state and local statutes and regulations, as well as permits, consent decrees and administrative orders applicable to the packaging of Diovan HCT (valsartan and hydrochorothiazide, USP) Combination Tablets at our Pharmaceutical production facility in Suffern, New York.

2/28/07

Joseph J. Affuso
Head, Health, Safety & Environment
Novartis Pharmaceuticals Corporation

Date

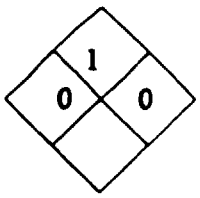
Non - Confidential

Diovan HCT™
Combination Tablets

Environmental Assessment Information

Appendix VI

ciba



MATERIAL SAFETY DATA SHEET

CIBA-GEIGY CORPORATION
PHARMACEUTICALS DIVISION
556 Morris Avenue
Summit, NJ 07901-1398

24 Hour Emergency Telephone Numbers:

Chemical Emergency Response Center:	1-800-888-8372
Medical Emergency:	1-908-277-5000
Non-Emergency Situation/Technical Information:	1-908-277-5397 (9:00 AM - 5:00 PM E.S.T.)

SECTION 1. PRODUCT IDENTIFICATION

PRODUCT NAME:	**Valsartan**
Ciba ID No.:	145765.4
CLASSIFICATION:	Class I Compound
SYNONYMS:	Diovan™ Active Ingredient, CGP 48933
THERAPEUTIC CATEGORY:	Antihypertensive agent (angiotensin II inhibitor)
GENERIC NAME:	None
CHEMICAL NAME:	(N)-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,,1'-biphenyl]-4-yl]methyl]-L-Valine
CHEMICAL FORMULA:	$C_{24}H_{29}N_5O_3$
MOLECULAR WEIGHT:	435.5

SECTION 2. COMPOSITION/INFORMATION ON INGREDIENTS

COMPOSITION	CAS #	CONCENTRATION (% BY WT.)
Valsartan	137862-53-4	> 99%

SECTION 3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

****

PRACTICALLY NON-TOXIC/ORAL
MAY DECREASE BLOOD PRESSURE
MAY BE HARMFUL BY INHALATION
AVOID CONTACT WITH EYES AND SKIN
AVOID BREATHING DUST

****

PRIMARY ROUTE(S) OF ENTRY: Inhalation

EFFECTS OF OVEREXPOSURE:

Skin:	Not known. Studies have not been performed to assess skin irritation potential.
Eye:	Not known. Studies have not been performed to assess eye irritation. Systemic effects from absorption is possible.
Inhalation:	Not known. Studies have not been performed to assess acute inhalation

icity. Systemic effects from absorption is possible.

Ingestion:	Although this material has been found to be well-tolerated in animals after oral administration, its pharmacological mode of action suggests that it

might possibly induce a variety of undesired effects.

TARGET ORGAN EFFECTS: Not known.

REPRODUCTIVE HAZARDS: There are no reported adverse effects on reproductive function or fetal development.

CARCINOGENICITY: Studies have not been performed to assess carcinogenic potential.

ACGIH:	Not listed
EPA:	Not listed
IARC:	Not listed
MAK:	Not listed
NIOSH:	Not listed
NTP:	Not listed
OSHA:	Not listed

MUTAGENICITY: Devoid of mutagenic potential in four test systems (see Section 11).

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: None known.

CTION 4. EMERGENCY AND FIRST AID MEASURES

Skin Contact:	Wash contaminated area with soap and water.
Eye Contact:	Flush with running water for 15 minutes holding eyelids open.
Inhalation:	Remove to fresh air. Restore and/or support breathing as needed.
Ingestion:	Get medical attention immediately.

SECTION 5. FIRE FIGHTING MEASURES

Flash Point: Not applicable **Method Used:** Not applicable

Flammable Limits (% in air)
Lower: Not applicable Upper: Not applicable

Autoignition Temperature: Not applicable
Extinguishing Media: Use media suitable for fire in surrounding area.
Special Fire Fighting Procedures and Precautions: Evacuate area and fight fire from safe distance.
Fire and Explosion Hazards: Contaminated water from fire hoses or sprinklers must be prevented from draining into waterways, sewers, or the ground water. Appropriate measures must be taken for

containment. Combustion can lead to the formation of poisonous and irritant decomposition products..

Fire-Fighting Equipment: Wear full protective clothing and a pressure-demand self-contained breathing apparatus.
Decomposition Products: Carbon and nitrogen oxides, as well as other poisonous or irritant gases and vapors can be formed following thermal decomposition or combustion.

NFPA Ratings: Health = 0 Flammability = 1 Reactivity = 0 Special Hazard = None
Hazard Rating Scales: 0 = Minimal 1 = Slight 2 = Moderate 3 = Serious 4 = Severe U = Unknown

SECTION 6. ACCIDENTAL RELEASE MEASURES

Steps to be taken if Material is Released or Spilled: Using appropriate protective equipment, sweep up and containerize spilled material. Avoid contamination of soils, sewage systems and waterways.

SECTION 7. HANDLING AND STORAGE

Storage Temperature (Min./Max.): Store material between 2°C and 30°C.
Shelf Life: Not known.
Special Sensitivity: Protect from light and warm, damp air.
Handling and Storage Precautions: Store in tightly sealed containers and protect from excessive heat and sources of ignition.

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Eye Protection: Safety glasses with side shields.
Skin Protection: Wear protective gloves if direct handling of material is expected. If in solution, selection of gloves depends upon vehicle.
Respiratory Protection: A NIOSH-approved half-face respirator equipped with dust filters must be worn for open handling of material. HEPA cartridges offer a greater level of protection.
Ventilation Requirements: Local exhaust ventilation should be used for dusty operations involving quantities greater than one kilogram.
Additional Measures: Handle as a Class I compound *(see Safety Procedure G-14)*. Avoid contact with eyes, skin and personal clothing.

Exposure Limits (Definition of terms):

ACGIH:	American Conference of Governmental Industrial Hygienists
Ceiling:	Ceiling Value
DTEL:	Derived Target Exposure Limit
MAK:	Federal Republic of Germany Maximum Concentration Values in the Workplace
NIOSH:	National Institute for Occupational Safety and Health
OSHA:	Occupational Safety and Health Administration [USA]
PEL:	Permissible Exposure Limit
PIEL:	Permissible Internal Exposure Limit [Ciba internal]
REL:	Recommended Exposure Limit
Skin (notation):	absorbed through skin
STEL:	Short Term Exposure Limit

TLV: Threshold Limit Values
TWA: Time-Weighted Average

Component	Exposure Limit
Valsartan	PIEL = 1 mg/m^3 (Ciba internal provisional 8 hr. TWA)

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance :	fine powder	**Odor Threshold:**	none
Color:	white	**Odor Characteristics:**	odorless
pH:	3.8 @ 0.18 g/l, 25°C (aq. sol.)	**Vapor Pressure:**	< 1 x 10^{-5} torr
Boiling Point:	not applicable	**Vapor Density:**	not applicable
Melting/Freezing Pt:	105 - 110°C (221 - 230°F)	**Specific Gravity:**	0.978
Solubility:	0.18 g/l in water (25°C);	**Partition Coefficient:**	-1.10 at 22°C
	> 300 g/l in 96% ethanol (26°C)	**Combustibility:**	brief ignition and
	> 500 g/l in methanol (26°C)		rapid extinction
Ignition Point:	410°C: whirled dust method	**Hazard Class (milling):**	SKM 1
Dust Explosion Class:	ST 2H	**Hazard Class (drying):**	SKT 1
Self-ignition:	none up to 105°C		

SECTION 10. STABILITY AND REACTIVITY

Stable (yes/no):	Yes. Decomposition occurs at 170°C. 1% aqueous solution is stable (at pH 7.4) for at least 3 weeks at 50°C.
Hazardous Polymerization:	Will not occur.
Conditions and Materials to Avoid:	Protect from excessive heat and moisture. Avoid storage of material below 2°C and above 30°C.
Incompatibility:	Avoid contact with acids, bases, and oxidizing agents.
Hazardous Decomposition Products:	Thermal decomposition or combustion results in the formation of carbon and nitrogen oxides, as well as other poisonous or irritant gases and vapors.

SECTION 11. TOXICOLOGICAL INFORMATION

Eye Irritation:	No data available.	
Skin Irritation/Sensitization:	No data available.	
Oral Toxicity:	LD_{50} > 2000 mg/kg	(rat)
	LD_{50} = 1000 mg/kg	(marmoset)
Dermal Toxicity:	No data available.	

Inhalation Toxicity: No data available.

Subchronic: In short-term studies over periods of 14 days in rats and marmosets and 3 months in rats, treatment with Valsartan in daily oral doses of 60, 200, or 600 mg/kg was generally well tolerated. The most prominent findings were elevated blood urea levels at doses $\geq$ 200 mg/kg in rats and at 600 mg/kg in marmosets.

Marmosets treated for 3 months with daily oral doses of 30, 60, 200, and 600 mg/kg displayed dose-related toxic effects at doses of 200 mg/kg and above. The high dose was reduced to 400 mg/kg after 23 days. The main pathological effects took the form of changes in renal function with increased blood urea and creatinine levels.

Repeated daily intravenous administration of Valsartan over 14 days at doses of 10, 30, or 100 mg/kg in rats and 6, 20, or 60 mg/kg in marmosets was generally well tolerated.

Chronic/Carcinogenicity: The results of 6- and 12-month oral studies in rats receiving 20, 60, and 200 mg/kg and in marmosets receiving 12, 40, and 120 mg/kg body weight indicated good tolerability. A few minor symptoms were presumed to be due to the pharmacological activity of the compound. In rats, some kidney values were altered at 60 and 200 mg/kg.

Mutagenicity: Negative in the following tests: Ames test; *Salmonella - E. coli* /liver microsome test; *in vitro* gene-mutation test with V79 cells (embryonic lung fibroblasts) of the Chinese hamster; *in vitro* chromosome aberration test in ovarian cells of the Chinese hamster; *in vivo* micronucleus test in rats.

Reproductive Effects: No teratogenic effects were detectable in the fetuses of rats and mice given doses up to and including 600 mg/kg daily, nor in those of rabbits given 10 mg/kg, the highest dose tolerated without toxic reactions in the dams. Treatment with doses up to and including 200 mg/kg also had no effect on the fertility or reproductive performance of one generation of rats and their offspring.

SECTION 12. ECOLOGICAL INFORMATION

Ecotoxicological Information

Microbial growth inhibition:

Species	Minimum Inhibitory Concentration (mg/L)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	> 1000
Bacillus subtilis	1000
Nostoc sp.	200

Freshwater Invertebrates: EC_{50} = 580 mg/L Species: *Daphnia magna*

	NOEC = 280 mg/L	Species: *Daphnia magna*
Fish toxicity:	LC_{50} > 100 mg/l (96 hours)	Species: trout

Chemical Fate Information:
Valsartan is not biodegradable (method of OECD guideline No. 301/B). When properly introduced into adequately prepared biological sewage-treatment plants, no reduction in the aerobic decomposition capacity of activated sludge is to be anticipated. Contamination of soil, drains, and surface waters should be avoided. Bioaccumulation in fish or other aquatic organisms, although unlikely to occur, cannot be ruled out.

SECTION 13. DISPOSAL CONSIDERATIONS

Waste Disposal Method: All wastes must be disposed of in accordance with local, state and federal laws and regulations. (Contact local or state environmental agency for specific rules).

EPA Hazardous Waste Number: None.

SECTION 14. TRANSPORTATION INFORMATION

DOT Shipping Name:	Drugs, N.O.I. NMFC Item 60000
DOT Hazard Class:	None
DOT Identification:	None
Packing Group:	None
Hazard Label:	None
Special Requirements:	None
Exceptions:	None
Non-Bulk Requirements:	None
Bulk Requirements:	None
Max. Passgr. Air/Rail:	None
Max. Cargo Only Air/Rail:	None
Reportable Quantity (lbs.):	None
Stowage:	None
Other Requirements:	None
Product Label:	None
Packing Group:	None

SECTION 15. REGULATORY INFORMATION

OSHA (Occupational Safety & Health Administration): This Material Safety Data Sheet contains the information required by the Federal OSHA Hazard Communication Standard (29 CFR 1910.1200).

OSHA PSM (Product Safety Management): Not listed

NJ TCPA (Toxic Catastrophe Prevention Act): This product contains NONE of the substances subject to the reporting requirements of Section N.J.A.C. 7:31 of this act.

TSCA (Toxic Substance Control Act): Not listed

CERCLA (Comprehensive Response Compensation & Liability Act): Not listed

SARA Title III (Superfund Amendments & Reauthorization Act):

Section 302 Extremely Hazardous Substances:	Not applicable (R&D exemption)
Section 311/312 Hazard Categories:	None
Section 313 Toxic Chemicals:	Not listed

RCRA (Resource Conservation & Recovery Act): Not listed

Other State Regulatory Information:

New Jersey: NJ RTK Threshold Planning Quantity = 10,000 lbs.

Other USA Regulations: None

California Proposition 65: The following statement is made in order to comply with the California Safe Drinking Water and Toxic Enforcement Act of 1986: *This material is not known to the State of California to cause cancer or reproductive toxicity.*

Canada: WHMIS Ingredient Disclosure List
Not listed

EEC Classification (European Economic Community):

Warning Symbol: Xn
Risk Codes: R20
Safety Codes: S24/25

SECTION 16. OTHER INFORMATION

Reason for Issue:
13 Mar 97 - Changed chemical name.
29 Aug 95 - Added tradename under Synonyms.

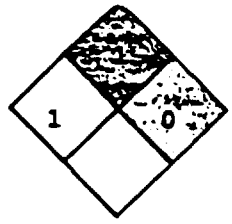
Supersedes Date: 30 Apr 96

Written By:	J. A. Sinno	**Date:**	13 Mar 97
Approved By:	J. A. Sinno	**Date:**	13 Mar 97

To the best of our knowledge, the information contained herein is accurate. However, Ciba-Geigy Corporation does not assume any liability whatsoever for the accuracy or completeness of the information contained herein except for the product's administration/use as intended. Final determination of the suitability of any material is the sole responsibility of the user. All materials may present unknown hazards and should be used with caution. Although certain hazards are described herein, we cannot guarantee that these are the only hazards which exist.

Material Safety Data Sheet

CIBA-GEIGY Corporation, Pharmaceuticals Division
Summit, New Jersey 07901



Material: Esidrix **Code Number:** 304463

Chemical Name: 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide **Synonyms:** Hydrochlorothiazide; Dichlotiazid; Aquarius; HCTZ; HCZ

Formula: $C_7H_8ClN_3O_4S_2$ MW =297.73 **DOT Number:** none

HAZARDOUS INGREDIENTS

Composition	CAS#	%	Exposure Limit
Hydrochlorothiazide	58-93-5	98-101.5	PIEL = 0.25 mg/m³ (DTEL)

HEALTH HAZARD INFORMATION

Primary Route(s) of Entry: Inhalation

Toxicity Data:
LD_{50} (oral-mouse) > 3,080 mg/kg
LD_{50} (dermal-rabbit) > 3,038 mg/kg
LC_{50} (inh-rat) > 925 mg/m³

1	CAUTION: SLIGHTLY TOXIC AFFECTS THE CARDIOVASCULAR SYSTEM MILD IRRITANT

Effects of Overexposure:
Esidrix is an antihypertensive and diuretic drug. Symptoms of overexposure include hypotension, headache, dizziness, blurred vision, vertigo and nausea. Esidrix is a mild eye irritant and may cause allergic reactions in sensitive individuals. Esidrix may also affect the developing fetus.

Emergency and First Aid Procedures: CONTACT EMPLOYEE HEALTH SERVICES IMMEDIATELY
Inhalation - Remove to fresh air.
Eye Contact - Flush with running water for at least 15 minutes.
Skin Contact - Wash contaminated area with soap and water.

SPECIAL PROTECTION INFORMATION

Ventilation: Use local exhaust as needed to control airborne dust.

Respiratory Protection: Wear a NIOSH-approved dust respirator equipped with HEPA cartridges. Use a full face respirator equipped with HEPA cartridges if dusty conditions exist.

Protective Gloves and Clothing: Rubber gloves. Wear disposable coveralls if dusty conditions exist.
Eye Protection: Safety glasses. Wear safety goggles (or full face respirator) if visible airborne dust is present.
Additional Measures: Wash up after handling this material.

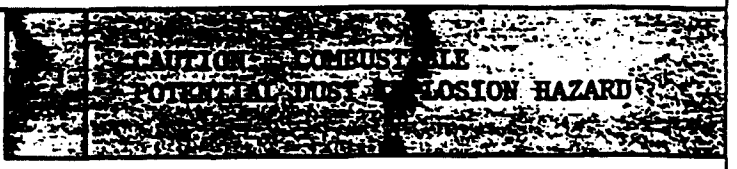
Material Safety Data Sheet - CIBA—GEIGY Corporation

PHYSICAL DATA

Appearance: White crystalline powder
Soluble In: Ammonia, ethanol, acetone
Melting Point: 273-275°C (523-527°F)
Boiling Point: not available

Odor Threshold: Odorless
Vapor Pressure (mm Hg): n.a.
Vapor Density (AIR = 1): n.a.
Specific Gravity (H_2O = 1): not avail.

FIRE AND EXPLOSION HAZARDS



Flash Point: not applicable
Flammable Limits (% in air)
Lower: n.a. Upper: n.a.
Autoignition Temperature: not applicable
Extinguishing Media:
Water, CO_2, or dry chemical.
Special Fire Fighting Procedures and Precautions:
Wear full protective clothing and self contained breathing apparatus.
Unusual Fire and Explosion Hazards: not available

REACTIVITY

Stability: Stable
Hazardous Polymerization:
Will not occur.

0	STABLE

Conditions and Materials to Avoid:
not available

Hazardous Decomposition Products:
not available

ENVIRONMENTAL PROTECTION

Steps to be taken if Material is Released or Spilled: Using appropriate protective equipment, sweep up spill and place in a container. Residuals may be flushed to the sanitary sewer with water.

Waste Disposal Method: All wastes will be sent to an appropriate, approved disposal facility following standard operating procedures.

EPA Hazardous Waste Number: none

SPECIAL PRECAUTIONS

Avoid skin contact. Repeated exposure may cause sensitization in some individuals.
See Physician's Desk Reference for more information.
Medical Conditions Aggravated by Exposure: Pre-existing kidney, liver, pancreatic and blood disease, anuria, or hypersensitivity to Esidrix.

Approval: Usha Wright Date: 3/2/88

IF YOU HAVE ANY QUESTIONS REGARDING THE HAZARDS ASSOCIATED WITH THE USE OF THIS MATERIAL, PLEASE CONTACT THE SAFETY AND INDUSTRIAL HYGIENE DEPARTMENT (201) 277-5397.

n.a.: not applicable