

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20148

CHEMISTRY REVIEW(S)

APR - 3 1993

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

NDA #: 20-148

DATE REVIEWED: 06-OCT-92

CHEMISTRY REVIEW #: 1

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	28-DEC-90	03-JAN-91	28-JAN-91
CORRESPONDENCE	23-JUL-92	24-JUL-92	27-JUL-92

NAME & ADDRESS OF APPLICANT:

SANDOZ RESEARCH INSTITUTE
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/Established/USAN:
Code Name/#:
Chem.Type/Ther.Class:

DHE 45
DIHYDROERGOTAMINE MESYLATE

ANDA Suitability Petition / DESI / Patent Status:

PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM:

STRENGTHS:

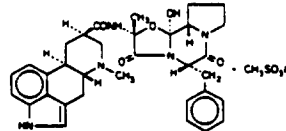
ROUTE OF ADMINISTRATION:

DISPENSED:

MIGRAINE
Nasal Spray
4 mg/ml
Nasal Spray
 Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

DIHYDROERGOTAMINE MESYLATE



CONCLUSIONS & RECOMMENDATIONS:

cc:

Org. NDA 20-148

HFD-120/Division File

HFD-120/WBrannon/10/7/92

HFD-120/CSO/KHiggins/

HFD-120/RCSultz

HFD-102/CKumkumiah [#1 only]

R/D Init by: SUPERVISOR

filename: F:\BRANNON\NDA20148.001

Wilson Brannon
Wilson Brannon, Review Chemist

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

DATE REVIEWED:

NDA/ANDA/AAA #: 20-148

CHEMISTRY REVIEW #: 2

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	28-DEC-90	03-JAN-91	28-JAN-91
AMENDMENT	23-JUL-92	24-JUL-92	27-JUL-92

AUG - 9 1993

NAME & ADDRESS OF APPLICANT:

Sandoz Research Institute
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/Established/USAN:
Code Name/#:
Chem.Type/Ther.Class:

DHE 45
Dihydroergotamine Mesylate

ANDA Suitability Petition / DESI / Patent Status:

PHARMACOLOGICAL CATEGORY/INDICATION:

Migraine

DOSAGE FORM:

Nasal Spray

STRENGTHS:

4 mg/ml

ROUTE OF ADMINISTRATION:

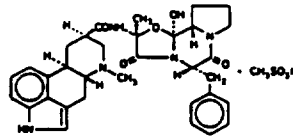
Nasal Spray

DISPENSED:

Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

DIHYDROERGOTAMINE MESYLATE



CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable under CGMPs because the finished drug product allows

cc:

Org. NDA 20-148
HFD-120/Division File
HFD-120/WBrannon/
HFD-120/CSO/KHiggins/
HFD-120/RCSchultz/ *128 F-5-93*

Wilson Brannon
Wilson Brannon, Review Chemist

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HFD-130

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

DATE REVIEWED:

NDA/ANDA/AAA #: 20-148

CHEMISTRY REVIEW #:

3

DEC - 2 1991

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	28-DEC-90	03-JAN-91	28-JAN-91
AMENDMENT	23-JUL-92	24-JUL-92	27-JUL-92

NAME & ADDRESS OF APPLICANT:

Sandoz Research Institute
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

Proprietary:

DHE 45

Nonproprietary/Established/USAN:

Dihydroergotamine Mesylate

Code Name/##:

Chem.Type/Ther.Class:

ANDA Suitability Petition / DESI / Patent Status:

PHARMACOLOGICAL CATEGORY/INDICATION: SAGE

DOSAGE FORM:

Nasal Spray

STRENGTHS:

4 mg/ml

ROUTE OF ADMINISTRATION:

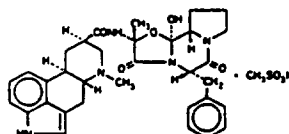
Nasal Spray

DISPENSED:

Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

DIHYDROERGOTAMINE MESYLATE



CONCLUSIONS & RECOMMENDATIONS:

I concur with the FDA laboratory findings

cc:

Org. NDA 20-148

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HFD-120/WBrannon/

HFD-120/CSO/DGrilley/

HFD-120/RCS Schultz/

HFD-80

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Wilson Brannon, Review Chemist

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

NDA 20-148

CHEMISTRY REVIEW #: 4

DATE REVIEWED: 03-MAR-95

<u>SUBMISSION TYPE</u>		<u>DOC DATE</u>
ORIGINAL	RS	16-JAN-92
AMENDMENT	BZ	29-MAY-92
	BC	20-JUL-94

<u>CDER DATE</u>	<u>ASSIGN DATE</u>
17-JAN-92	17-JAN-92
02-JUN-92	02-JUN-92
21-JUL-94	21-JUL-94

NAME & ADDRESS OF APPLICANT:

SANDOZ RESEARCH INSTITUTE
59 Route 10
East Hanover, N. J. 07936-1080

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/Established/USAN:

Code Name/#:

Chem.Type/Ther.Class:

MIGRAMIST
DIHYDROERGOTAMINE MESYLATE
DHE-45
3 S

PHARMACOLOGICAL CATEGORY/INDICATION: MIGRAINE

DOSAGE FORM:

AMPULE

STRENGTHS:

4 mg/mL

ROUTE OF ADMINISTRATION:

NASAL SPRAY

DISPENSED:

XXX Rx ___ OTC

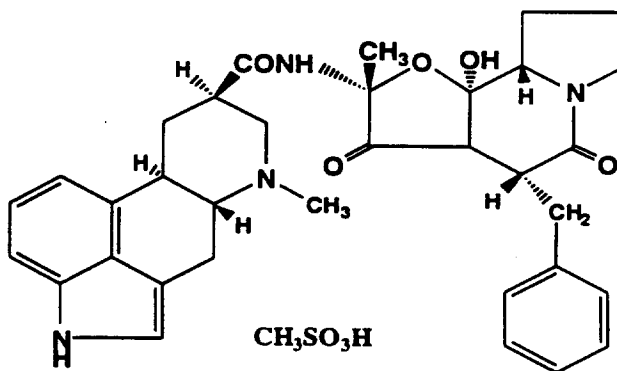
CHEMICAL NAME, STRUCTURAL FORMULA, MOL. FORMULA, MOL.WT.:

DIHYDROERGOTAMINE MESYLATE

(5' α)-9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-Ergotaman-3',6',18-trione monomethanesulfonate (salt)

C₃₃H₃₇N₅O₅ • CH₄O₃S

Mol. Wt. = 679.8



CONCLUSIONS & RECOMMENDATIONS:

NDA 20-148 is APPROVABLE for Chemistry

cc:

Org. NDA20-148
HFD-120/Division File
HFD-/RNighswander
HFD-120/WLBrannon
R/D Init by: SWB

AWB 3/3/95

Wilson L. Brannon

Wilson-L. Brannon, Review Chemist
filename: N020148 R-4

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

DATE REVIEWED: 03-MAR-95

NDA/ANDA/AAA #: **20-148**

CHEMISTRY REVIEW #: 5

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL RS	16-JAN-92	17-JAN-92	
AMENDMENT BC	12-APR-95	14-APR-95	14-APR-95

NAME & ADDRESS OF APPLICANT:

SANDOZ RESEARCH INSTITUTE
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

Proprietary:

MIGRANAL

Nonproprietary/Established/USAN:

Dihydroergotamine Mesylate

Code Name#:

DHE-45

Chem.Type/Ther.Class:

3 S

ANDA Suitability Petition / DESI / Patent Status:

JUN - 7 1995

PHARMACOLOGICAL CATEGORY/INDICATION:

MIGRAINE

DOSAGE FORM:

AMPULE

STRENGTHS:

4 mg/mL

ROUTE OF ADMINISTRATION:

NASAL SPRAY

DISPENSED:

___ Rx ___ OTC

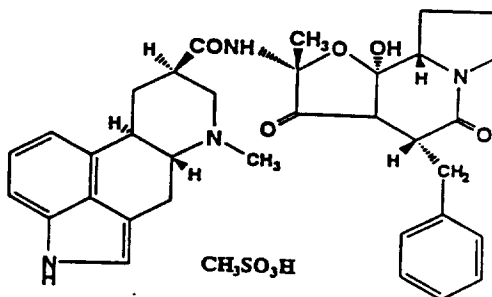
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

DIHYDROERGOTAMINE MESYLATE

(5' α)-9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-Ergotaman-3',6',18-trione monomethanesulfonate (salt)

$C_{23}H_{27}N_2O_5 \cdot CH_4O_3S$

Mol.Wt. = 679.8



CONCLUSIONS & RECOMMENDATIONS:

Response to deficiencies (01-MAR-95) acceptable.

cc:

Org. NDA 20-148
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HFD-120/SUPERVISOR/SWBlum/
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Wilson Brannon
Wilson Brannon, Review Chemist

AMB 6/6/95

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DEC 30

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

DATE REVIEWED: 18-DEC-96

NDA/ANDA/AAA #: 20-148

CHEMISTRY REVIEW #: 6

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	RS 16-JAN-92	17-JAN-92	
	N(RS) 17-MAY-96	20-MAY-96	

NAME & ADDRESS OF APPLICANT: SANDOZ RESEARCH INSTITUTE
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME
Proprietary: MIGRANAL
Nonproprietary/Established/USAN: Dihydroergotamine Mesylate
Code Name/#: DHE-45
Chem.Type/Ther.Class: 3 S

ANDA Suitability Petition / DESI / Patent Status:

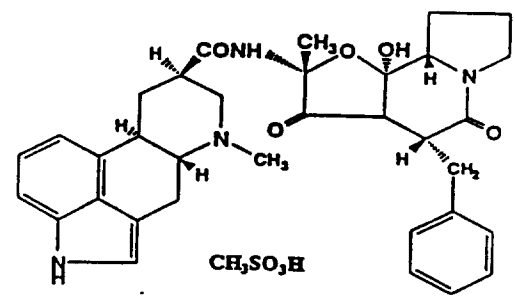
PHARMACOLOGICAL CATEGORY/INDICATION: MIGRAINE

DOSAGE FORM: AMPULE
STRENGTHS: 4 mg/mL
ROUTE OF ADMINISTRATION: NASAL SPRAY
DISPENSED: ___ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

DIHYDROERGOTAMINE MESYLATE
(5 α)-9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-Ergotaman-3',6'-trione monomethanesulfonate (salt)

C₃₃H₃₇N₅O₅ • CH₄O₃S
Mol.Wt. = 679.8



CONCLUSIONS & RECOMMENDATIONS:
This submission primarily contains pharmacology, toxicology, and clinical information.

cc:
Org. NDA 20-148
HFD-120/Division File
HFD-120/WBrannon/
HFD-120/CSO/RNighswander/
HFD-120/SUPERVISOR/SWBlum/
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Wilson Brannon
Wilson Brannon, Review Chemist

AMPB
12/16/96

JUL 16 1997

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

NDA/ANDA/AAA #: 20-148

DATE REVIEWED: 16-JUL-97

CHEMISTRY REVIEW #: 7

SUBMISSION TYPE DOCUMENT DATE

CDER DATE ASSIGNED DATE

ORIGINAL RS 16-JAN-92
 N(RS) 17-MAY-96
 AMEND 13-JUN-97

17-JAN-92
20-MAY-96
16-JUN-97 16-JUN-97

NAME & ADDRESS OF APPLICANT:

SANDOZ RESEARCH INSTITUTE
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/Established/USAN:
Code Name/#:
Chem.Type/Ther.Class:

MIGRANAL
Dihydroergotamine Mesylate
DHE-45
3 S

ANDA Suitability Petition / DESI / Patent Status:

PHARMACOLOGICAL CATEGORY/INDICATION:

MIGRAINE

DOSAGE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION:

DISPENSED:

AMPULE
4 mg/mL
NASAL SPRAY
___ Rx ___ OTC

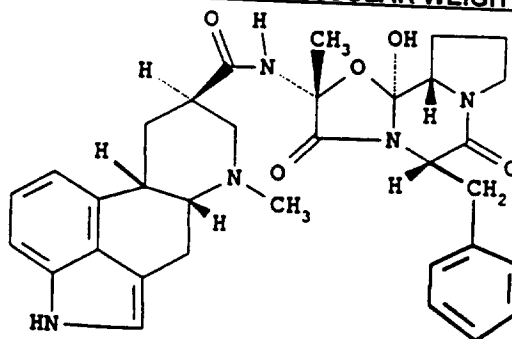
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

DIHYDROERGOTAMINE MESYLATE

(5 α)-9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-Ergotaman-3',6'18-trione monomethanesulfonate (salt)

C₃₃H₃₇N₄O₅ • CH₄O₃S

Mol.Wt. = 679.8



CONCLUSIONS & RECOMMENDATIONS:

This submission primarily contains pharmacology and clinical information in the package insert. In the "HOW SUPPLIED" section the storage statement correctly reads "Store below 77°F (25°C). Do not refrigerate or freeze". NDA 20-148 is APPROVABLE. The EA package has been completed. EER update status is ACCEPTABLE on 5-AUG-96.

cc:

Org. NDA 20-148
HFD-120/Division File
HFD-120/WBrannon/
HFD-1 [redacted]
HFD-120/SUPERVISOR/SWBlum/
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Wilson Brannon, Review Chemist

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ON ORIGINAL

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1/16/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20148

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR
[DHE-45 NASAL SPRAY]
[Dihydroergotamine Mesylate]
[4mg/ml]
NDA 20-148

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION HFD-120

FINDING OF NO SIGNIFICANT IMPACT
NDA 20-148
MIGRAMIST NASAL SPRAY
(4 MG/ML)

The Food and Drug Administration [FDA] recognizes the National Environmental Policy Act of 1969 [NEPA] as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

In support of their new drug application for Migramist Nasal Spray, Sandoz Pharmaceutical Corporation has prepared an environmental assessment [21 CFR 25.31 a(a)]. This assessment includes the synthesis of the drug substance formulation and packaging of the drug product, and the use of the product. Dihydroergotamine mesylate is synthesized by Sandoz Pharma Ltd., CH-4002 Basle, Switzerland. The Basle Canton and Sandoz Pharma certify that the manufacturing facility operates in full compliance with relevant Swiss environmental law. The manufacture of the drug product, Migramist Nasal Spray, will be at Sandoz Pharmaceuticals Corporation, East Hanover, New Jersey. The production and packaging of Migramist Nasal Spray will not require expansion of facilities nor installation of new equipment. The two routes by which dihydroergotamine can enter the environment are: (1) use and elimination of the drug by human patients and (2) release of waste water from the Sandoz facility at East Hanover, New Jersey. Dihydroergotamine mesylate is a non-volatile solid, hence no measurable concentrations in the atmosphere. Four environmental and effects studies have been conducted with dihydroergotamine mesylate: (1) Growth Inhibition to Green Algae, (2) Inhibitory Concentration to Aerobic Bacteria, (3) Daphnia Acute Toxicity, and (4) Rainbow Trout Acute Toxicity.

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

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.

6/8/95
DATE

Wilson Brannon
PREPARED BY
Wilson Brannon
Review Chemist
Division of Neuropharmacological Drug Products

6/8/95
DATE

Stanley W. Blum
DIVISION CONCURRENCE
Stanley W. Blum, Ph.D.
Supervisory Chemist
Division of Neuropharmacological Drug Products

6/19/95
DATE

Nancy B. Say
Approved Phillip G. Vincent, Ph.D.
Environmental Assessment Officer Scientist
Center for Drug Evaluation and Research

6/20/95
DATE

Robert A. Jerussi
Concurrence
Robert Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

NON CONFIDENTIAL
ENVIRONMENTAL ASSESSMENT

DHE-45 NASAL SPRAY

NDA No. 20-148

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1. **DATE**

March 24, 1995

2. **NAME OF APPLICANT**

Sandoz Pharmaceuticals Corporation

3. **ADDRESS**

59 Route 10

East Hanover, New Jersey 07936

4. **DESCRIPTION OF THE PROPOSED ACTION**

4.1 **REQUESTED APPROVAL**

The proposed action includes synthesis of the drug substance, formulation and packaging of the drug product, and use of the product designated in this Environmental Assessment (EA) as DHE-45® Nasal Spray. The drug substance in this product is dihydroergotamine mesylate. The spray formulation will contain 4 mg of drug substance per milliliter of aqueous vehicle and the immediate container is a 1 mL amber ampule. The metered spray delivery system is hand-pump powered and no propellants are employed.

This is the official public version of the EA submitted as part of the New Drug Application (NDA No. 20-148) for DHE-45® Nasal Spray. Its format is arranged as required by 21 CFR 25.31a. Nonconfidential supporting documents for the items discussed in this EA have been organized as appendices in Section 15.

4.2 **NEED FOR ACTION**

The proposed action will provide a new dosage form of dihydroergotamine mesylate nasal spray (DHE) as a topical treatment for migraine headache. While I.V. and I.M. injectable treatments are available (DHE-45® Injection, Sandoz, approved NDA No. 5-929), they are inconvenient for patient home use.

Other drugs are also available for treatment of migraine such as the closely

structurally related ergotamine tartrate (Cafergot® Tablets, Sandoz). The safety profile of dihydroergotamine tartrate, however, due to somewhat lessened vasoconstrictive activity and the reduced incidence of nausea and vomiting, is thought to be an advantage, particularly for the proposed nasal spray formulation.

4.3 LOCATION OF PRODUCTION

Dihydroergotamine mesylate is synthesized by Sandoz Pharma Ltd., CH-4002 Basle, Switzerland. The Basle Canton and Sandoz Pharma certify that the manufacturing facility operates in full compliance with relevant Swiss environmental law (Appendix B-1 and B-2).

The drug substance will be shipped to Sandoz Pharmaceuticals Corporation, 59 Route 10, East Hanover, New Jersey, where (after review of the Certificate of Analysis and performance of an identifying test) it will be formulated and packaged for distribution.

4.4 LOCATIONS OF USE AND DISPOSAL

As prescribed medication for migraine headache, this drug will be ingested and eliminated wherever the patients spend their day. The amount that is eliminated (or excreted) will enter municipal treatment systems throughout the United States. At the Sandoz facility in East Hanover, process water and washdown water are sewered to the Hanover Sewerage Authority and to the Parsippany-Troy Hills Sewerage Authority. Nonaqueous and solid waste--as well as off-specification material--will be collected and shipped offsite for incineration at an EPA-permitted facility. Any amount of the drug substance that is utilized for laboratory testing at East Hanover would also be accumulated and sent offsite for incineration. Returned drug product (past expiration date) will be sent to Sandoz Pharmaceuticals in Lincoln, Nebraska for accumulation and classification, and sent offsite for incineration as a solid waste (Environmental Health Systems, Lincoln, Nebraska).

4.5 ENVIRONMENTAL SETTING OF FACILITIES

The land surrounding the 185-acre Sandoz property is being used for commercial and industrial complexes and residential development. The property is situated south of

and industrial complexes and residential development. The property is situated south of New Jersey Route 10. A number of other commercial and industrial complexes are also located along Route 10. Directly south of the site there is a residential development which is separated from the site by an area of deciduous woodland. A more detailed description of the environmental setting is provided in Appendix C.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THE PROPOSED ACTION

The new product for which this application is prepared is DHE-45 Nasal Spray. The relevant drug substance is dihydroergotamine mesylate. Its structure is shown in Figure 5-1.

5.1 NOMENCLATURE

5.1.1 Chemical Name

Dihydroergotamine mesylate

9,10-Dihydro-12'-hydroxy-2'methyl-5' α -(phenylmethyl)ergotaman-3',6'-18-trione
methanesulfonate

5.1.2 CAS Registry Number

6190-39-2

511-12-6 (free base)

5.1.3 Molecular Formula and Weight

$C_{33}H_{37}N_5O_5 \cdot CH_3SO_3H$ MW = 679.8

5.2 PHYSICAL DESCRIPTION

The drug substance, dihydroergotamine mesylate is a white to off-white crystalline powder, having little or no odor. Its chemical and physical properties are listed in Table 5-1.

Figure 5-1
Structure of Dihydroergotamine Mesylate

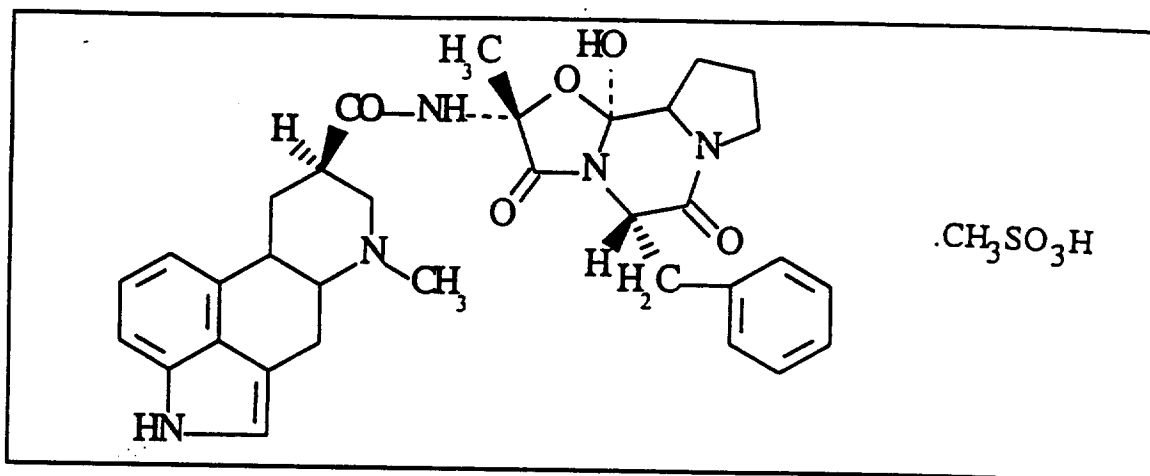


Table 5-1
Chemical and Physical Properties of Dihydroergotamine Mesylate

Molecular Formula	$C_{33}H_{37}N_5O_5 \cdot CH_3SO_3H$
Molecular Weight	679.8 g/mol
CAS Number	6190-39-2
Melting Point	230 - 235 °C
Solubility (w/v)	
water	0.84%
pH 5.5	0.065%
pH 6.8	0.001%
Ultraviolet/visible Spectrum	221 nm 281 nm 292 nm
pKa (ethanol/water 1:1)	6.35

5.3 ADDITIVES OR IMPURITIES

DHE-45 is sensitive to thermal degradation. In solution, the drug substance is also susceptible to oxidation and photodegradation. For this reason, the drug product is sparged, sterile-filtered and filled under carbon dioxide into amber glass ampules. No individual unknown may be greater than 0.5% and total unknowns no more than 2%. Moreover, total known by products and degradation products can account for no more than 5% and the sum of all impurities must be less than or equal to 8%.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 SUBSTANCES GENERATED DURING MANUFACTURING

The only solvent that will be used in the production of DHE-45[®] Nasal Spray is USP water for injection. No volatile organics will be released to the atmosphere. Very little dust will be generated as there is no granulation step in the manufacturing process. Trace quantities of drug substance will be sewerage as a result of equipment washdown. Wastewater from the Sandoz facility is sewerage to the Hanover Sewerage Authority and the Parsippany-Troy Hills Sewerage Authority. The wastes generated by packaging are drummed for transport and incineration by a licensed waste contractor.

6.2 CONTROLS EXERCISED ON RESIDUALS AND EMISSIONS

Sandoz Pharmaceuticals is in compliance with all emission requirements set forth in permits applicable to the production of DHE-45 Nasal Spray at its facility in East Hanover, New Jersey.

Air: The production facility (where the drug will be formulated) is equipped with a dust collector system (bag house) that is about 99 percent efficient. The baghouse system meets the state-of-the-art control requirements for particulate emissions. In addition to the bag house, HEPA filters are used throughout the manufacturing process. The air emissions fall under New Jersey Department of Environmental Protection and Energy (NJDEPE) Volatile Emission Regulations (N.J.A.C. 7:27).

Water: Process water and washdown water from the East Hanover facility are sewered to Hanover Sewerage Authority and Parsippany-Troy Hills Sewerage Authority. Wastewater from manufacturing passes through a skimmer pit that contains two 25,000-gal holding tanks. The primary purpose of these tanks is spill control, but they also moderate the flow of wastewater to rates acceptable for sewage treatment plants

Detention basins have been constructed for the production site. The basins were designed for storm water and fire-fighting water management at the facility. Surface water from the site, as well as cooling water from manufacturing, enters the basins through a sluice gate and must pass through a multi-media filtration system before being discharged into the Whippany River. In the event of a spill or fire, a gate at the outfall will be closed from a remote command center, allowing the containment of any contaminated water. These detention basins operate in compliance with NJPDES Discharge to Surface Water Permit No. 0001155.

Solid Waste: Nonaqueous and solid waste -- as well as off-specification material-- will be collected and shipped offsite for incineration at an EPA-permitted facility. A Waste Facility Audit Program has been instituted by Sandoz to insure the proper handling of solid wastes at such facilities. Returned product (past expiration date) will be accumulated at Sandoz Pharmaceuticals Corporation in Lincoln Nebraska and incinerated by Environmental Health Systems, Lincoln, Nebraska.

Worker Safety : Personnel in all Sandoz production facilities are provided with the appropriate personal protective equipment including safety glasses, safety shoes, protective gloves and clothing. Respiratory equipment is provided when appropriate, and respirators are accessible to personnel for use in non-routine and emergency situations. The facilities and equipment are designed to minimize employee exposure to airborne materials--including dust, vapors and fumes--through sound work practices as well as engineering and administrative controls.

All employees are trained in the proper operation of equipment in order to minimize potential safety, health and environmental risks. Extensive safety training is mandated at the facility, and Material Safety Data Sheets are available to personnel for all chemicals

handled in the manufacturing areas. Industrial hygiene monitoring of exposure to hazardous materials is routinely conducted. Personnel participate in periodic physical evaluations and are treated for all work related conditions at no cost to the employee.

The safe transport of all Sandoz drug-related materials is ensured by following protocols which include the training of Sandoz personnel and rigid specification of containers and materials. Access to drug substances and products is restricted to authorized personnel. In addition, access to the East Hanover site is carefully controlled and the premises are protected by a 24-hour security force. Sandoz has a fire brigade and hazardous materials team, the latter responds to spills and other emergencies involving hazardous materials.

6.3 COMPLIANCE OF PROPOSED ACTION WITH APPLICABLE EMISSION REQUIREMENTS

6.3.1 Atmospheric Emissions

The emissions generated during the manufacturing of this product were discussed in Section 6.1. The U.S. Environmental Protection Agency (USEPA) and the New Jersey Department of Environmental Protection and Energy (NJDEPE) regulate the air emissions at Sandoz in East Hanover. At the federal level, the Clean Air Act Amendments of 1990 are the primary statutes governing the regulation of volatile organic compounds (VOCs) and hazardous air pollutants (HAPs).

The State of New Jersey has also issued regulations concerning air emissions:

New Jersey Administrative Code

- N.J.A.C. 7:27-6 Control and Prohibition of Particles from Manufacturing Process.
- N.J.A.C. 7:27-8 Permits and Certificates.
- N.J.A.C. 7:27-16 Control and Prohibition of Air Pollution by Volatile Organic Compounds.

- N.J.A.C. 7:27-17 Control and Prohibition of Air Pollution by Toxic Substances.
- N.J.A.C. 7:27-19 Control and Prohibition of Air Pollution from Oxides of Nitrogen.
- N.J.A.C. 7:27-21 Emission Statements.

A list of the current New Jersey Air Quality permits for pharmaceutical manufacturing in Building 415 in East Hanover is provided in Appendix D. These permits are in the form of Temporary Permits to Operate Control Apparatus or Equipment and are subject to automatic 90 day extensions.

6.3.2 Releases to Sewage Treatment Plants

The Sandoz facilities in East Hanover are subject to and in compliance with current effluent guidelines and standards for pharmaceutical manufacturing. All process and sanitary wastewater is discharged to local treatment plants in accordance with industrial discharge permits. The majority of the wastewater (50-85 %) is discharged to the Hanover Sewerage Authority in accordance with Industrial Permit No. D-15. The remainder is discharged to the Parsippany-Troy Hills Sewerage Authority in accordance with NJPDES/Significant Industrial User (SIU) Permit No. 0081710. The permits and their monitoring requirements are provided in Appendix E. Analyses for wastewater monitoring are performed using USEPA-accepted protocols.

6.3.3 Occupational Environment

All chemicals used in manufacturing in East Hanover are regulated by the Occupational Safety and Health Administration under its responsibility for (1) permissible exposure limits, (2) safe handling of flammable liquids, (3) safe handling of corrosives, and (4) hazard communication. Handling procedures specified in the Material Safety Data Sheets are followed throughout all operations.

Applicable Federal, State, and local regulations pertaining to the safe handling of chemicals at Sandoz in East Hanover are as follows:

U.S. Occupational Safety and Health Act

New Jersey Toxic Catastrophe Prevention Act N.J.A.C. 7:31

New Jersey Worker and Community Right-To-Know Law--N.J.S.A. 34:5A-1 Et. Seq.

New Jersey Department of Health Regulations

6.3.4 Solid/Hazardous Waste Transportation and Disposal

The United States Environmental Protection Agency (USEPA) and the New Jersey Department of Environmental Protection and Energy (NJDEPE) regulate the generation, treatment, storage, transportation and disposal of all waste material generated at Sandoz in East Hanover. At the federal level, the Resource Conservation and Recovery Act (RCRA) of 1976 is the primary statute governing the regulation of solid and hazardous material. New Jersey has issued regulations concerning waste materials under the New Jersey Solid Waste Management Act. The United States Department of Transportation (USDOT) regulates the transport of hazardous material under the Hazardous Material Transportation Act (HMTA) of 1975 and the Hazardous Material Transportation Uniform Safety Act (HMTUSA) of 1990. These regulations are codified as follows:

Resource Conservation and Recovery Act (RCRA) 40 CFR Parts 240-280

New Jersey Solid Waste Management Act N.J.A.C. 7:26

HMTA and HMTUSA 49 CFR Parts 101-179

6.4 EFFECT OF PROPOSED ACTION ON COMPLIANCE WITH CURRENT EMISSION REQUIREMENTS

The production and packaging of DHE-45 Nasal Spray will not require expansion of facilities nor installation of new equipment. The manufacturing process will be scheduled to fit within the existing framework of activities for which current emission requirements are applicable. A statement of compliance with all federal, state and local

safety and environmental regulations pertinent to the production of DHE-45 Nasal Spray by Sandoz in East Hanover is provided in Appendix F.

6.5 AMOUNT OF DIHYDROERGOTAMINE ENTERING THE ENVIRONMENT

The two routes by which dihydroergotamine can enter the environment are: (1) use and elimination of the drug by human patients and (2) release of wastewater from the Sandoz facility at East Hanover, New Jersey. The second route is insignificant; only trace quantities of drug substance will be sewerred during the production process. Calculations for the amount of dihydroergotamine and its metabolites entering the environment as a result of patient use are combined as if the drug substance (alone) were being eliminated.

To conservatively (i.e., maximally) estimate the amount of dihydroergotamine eliminated by patients to a typical wastewater treatment plant, it is assumed that the production forecast for the United States during the fifth year of sales will be equal to the amount of the drug that is ingested and eliminated by the U.S. population. The estimated concentration of DHE at a typical wastewater treatment plant (resulting from elimination by human patients) would be less than 0.005 $\mu\text{g/L}$.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Dihydroergotamine (DHE) will be introduced to the environment via patient use; from human patients to wastewater treatment plants throughout the United States. In the water of a sewage treatment facility, or potentially in the surface water that dilutes the effluent, DHE is expected to be degraded by environmental processes that include photolysis, oxidation, and biodegradation. These processes are evaluated below. However, if processes leading to abatement are not considered, a worst case concentration for surface water can be estimated.

From Section 6.5, the concentration at a typical wastewater treatment plant that would be due to human elimination would be less than 0.005 $\mu\text{g/L}$. Because of variations

in plant capacity and in rates of surface water flow, dilution factors throughout the United States can vary (depending on geographic location) from about 10^{-7} to essentially no dilution (i.e., settling ponds or intermittently dry drainage channels) (Metcalf & Eddy, Inc., 1979; Linsley et al., 1975). A typical dilution factor for many rivers of the United States is 10^{-3} and, thus, typical concentrations in surface waters that receive sewage plant effluent would be less than 0.005 ng/L. It should be noted, however, that the concentration would be much less downstream from the effluent outfall.

The primary (or first) pathway of degradation for DHE is expected to occur at wastewater treatment plants. A Modified Sturm Test of Ready Biodegradability showed that DHE was readily biodegradable. The extent of biodegradation, calculated as percentage of measured dissolved carbon, was 95% (DOC/DOC) in 13 days, demonstrating nearly complete mineralization (to carbon dioxide and water).

In the unlikely event that any quantity of DHE was released unchanged into surface waters, it should be rapidly degraded via aqueous photolysis and/or oxidation. The electromagnetic absorption spectrum of the drug substance exhibits an absorption (292 nm) within the wavelength range of terrestrial sunlight. Furthermore, photodegradation of formulated material (in aqueous solution) has been observed, and is expected to occur in surface waters. To stabilize the drug product from oxidative degradation, the formulated solution is sparged and filled under CO_2 into amber glass ampules and flame sealed. The sensitivity of DHE to oxidation provides an additional route for degradation of the drug substance in the environment.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Four environmental effects studies have been conducted with dihydroergotamine mesylate: (1) Growth Inhibition to Green Algae, (2) Inhibitory Concentration to Aerobic Bacteria, (3) *Daphnia* Acute Toxicity, and (4) Rainbow Trout Acute Toxicity. These studies were conducted in accordance with the Organization for Economic Cooperation and Development (OECD) guidelines in compliance with Good Laboratory Practice (GLP) Regulations. The results are presented in Table 8-1.

The lowest no-observed-effect concentration (NOEC) for all tested organisms is the value for static, 48-hour toxicity of daphnia, 9.7 mg/L. The next highest NOEC (NOEbC) is 11 mg/L for algal growth inhibition. The NOECs for inhibitory concentration to aerobic bacteria and acute toxicity (96 hr) to Rainbow Trout are > 100 mg/L.

The worst-case (no degradation) concentration of DHE at a typical sewage treatment facility would be less than 0.005 $\mu\text{g/L}$, and the corresponding concentration in a typical river would be less than 0.005 ng/L. These concentrations are about six to nine orders of magnitude less than the lowest toxic effect of the drug substance. Thus, it is obvious that the worst-case concentrations (assuming no degradation) of DHE in the environment that could potentially result from approval of the proposed action will not have an adverse effect on living organisms.

9. USE OF RESOURCES AND ENERGY

The proposed action does not require a large commitment of resources. The processing that will be involved in formulating and packaging of DHE-45 Nasal Spray will be a very minor activity at East Hanover. Moreover, no irreversible or irretrievable commitment of limited national resources will be involved.

The State of New Jersey does not regard any property in the vicinity of the manufacturing location identified in Section 4.3 to have historical or archaeological importance.

10. MITIGATION MEASURES

Emission standards at East Hanover are described in Section 6.2. Compliance of the proposed action with applicable emission requirements at East Hanover is discussed in Section 6.3. Safe handling and cleanup procedures are provided in the Material Safety Data Sheet (Appendix G).

TABLE 8-1

Toxicity Testing of Dihydroergotamine Mesylate with Representative Environmental Organisms

Test Organism	Conditions	Results	Study Report
Green Algae (<i>Scenedesmus subspicatus</i>)	Growth Inhibition (OECD 201) Paris, 1984	EbC ₅₀ > 100 mg/L (72 hr) NOEbC 11 mg/L (72 hr)	Appendix B-3
Aerobic Bacteria (Activated Sludge)	Inhibitory Concentration (OECD 209) April 1984	EC ₅₀ > 100 mg/L (3 hr) EC ₂₀ > 100 mg/L (3 hr) EC ₁₀ > 100 mg/L (3 hr)	Appendix B-4
Water Flea (<i>Daphnia magna</i>)	Acute toxicity (OECD 202) April, 1984	NOEC 9.4mg/L (48 hrs) EC ₅₀ 113 mg/L (48 hr)	Appendix B-5
Rainbow Trout (<i>Oncorhynchus mykiss</i>)	Acute toxicity (OECD 203) Paris, 1992	NOEC > 100 mg/L (96 hr) LC ₅₀ > 100 mg/L (96 hr)	Appendix B-6

NOEC = the concentration at which no effects are observed.
 EC₅₀ = the concentration that produces an effect (e.g., death) in 50 percent of the population being tested.
 LC₅₀ = the lowest concentration that produces an effect in 50 percent of the population being studied.
 EbC₅₀ = the concentration that produces an effect in 50 percent of the population.

The manufacture of DHE-45 Nasal Spray will not significantly impact the environment. No volatile organics are used in the processing of the drug substance and only trace quantities are expected to be emitted to wastewater. Solid wastes from manufacturing and returned goods that contain dihydroergotamine mesylate will be destroyed in EPA-permitted incinerators.

11. ALTERNATIVES TO THE PROPOSED ACTION

The alternative to the proposed action, the manufacture, distribution and consumption by patients of DHE-45 Nasal Spray is no action. The no action alternative would deny the migraine headache patient population the opportunity to benefit from a new highly effective and convenient treatment.

12. PREPARER

This Environmental Assessment was prepared by Patricia McGovern, Assistant Director, Environmental Assessments, Sandoz Pharmaceuticals Corporation. She is an organic chemist who was previously employed at PTRL-WEST, a contract laboratory in Richmond, California, where she directed environmental fate studies of pesticides to support registration with EPA.

13. CERTIFICATION

The undersigned certifies that the information presented in this Environmental Assessment is true, accurate and complete to the best of the knowledge of Sandoz Pharmaceuticals Corporation, 59 Route 10, East Hanover, New Jersey.

Signature

John Taylor
John Taylor, PhD

Date

4-11-95

Title

Director, Regulatory Manufacturing and Controls

14. REFERENCES *

Linsley, R.K., Jr., Kohler, M.A., and Paullus, J.L.H., 1975. Hydrology for Engineers, 2nd Edition, New York: McGraw-Hill Book Company.

Metcalf & Eddy, Inc., 1979. Wastewater Engineering: Treatment, Disposal, Reuse. Revised by G. Tchobanoglous. New York: McGraw-Hill Book Company.

Pharmaceutical Manufacturers Association, 1991. Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA. Washington, D.C., July 1991.

* not provided

15. APPENDICES

- A:- SUMMARY OF ENVIRONMENTAL FATE AND EFFECT DATA FOR DIHYDROERGOTAMINE MESYLATE
- B-1: SWISS GOVERNMENT CERTIFICATION OF COMPLIANCE FOR PRODUCTION OF DIHYDROERGOTAMINE MESYLATE AT SANDOZ, BASEL, SWITZERLAND
- B-2: SANDOZ PHARMA STATEMENT OF COMPLIANCE FOR PRODUCTION OF DIHYDROERGOTAMINE MESYLATE AT SANDOZ, BASEL, SWITZERLAND
- C: ENVIRONMENTAL SETTING OF SANDOZ PHARMACEUTICALS, EAST HANOVER, NEW JERSEY
- D: CURRENT NEW JERSEY AIR QUALITY PERMITS
- E: WASTEWATER PERMITS
- F: CERTIFICATE OF COMPLIANCE
- G: MATERIAL SAFETY DATA SHEET FOR DIHYDROERGOTAMINE MESYLATE

APPENDIX A

**SUMMARY OF ENVIRONMENTAL FATE AND EFFECT DATA FOR
DIHYDROERGOTAMINE MESYLATE**

Appendix A¹

Summary of Environmental Fate and Effect Data

Test Material: Dihydroergotamine Mesylate

Molecular Formula: $C_{33}H_{37}N_5O_5 \cdot CH_3SO_3H$

Maximum Expected Emitted Concentration: 1.19×10^{-6} ppm (0.00119 $\mu\text{g/L}$)

Study Type	Results	Reference ¹
Water Solubility	water 0.84 % (w/w) pH 5.5 0.065 % (w/w) pH 6.8 0.001 % (w/w)	Appendix B-1
Ultraviolet/visible spectrum	221 nm 281 nm 292 nm	Appendix B-1
pKa (ethanol/water 1:1)	6.35	Appendix B-1
Aqueous Biodegradation (Sturm Ready Biodegradability)	95 % (DOC/DOC) (13 days)	Appendix B-2
Growth Inhibition to Green Algae (<i>Scenedismus subspicatus</i>)	EbC ₅₀ > 100 mg/L (72 hr) NOEbC ₅₀ 11 mg/L (72 hr)	Appendix B-3
Inhibitory Concentration to Aerobic Bacteria (Activated Sludge)	EC ₅₀ > 100 mg/L (3 hr) EC ₅₀ > 100 mg/L (3 hr) EC ₅₀ > 100 mg/L (3 hr)	Appendix B-4
Acute Toxicity to <i>Daphnia magna</i>	EC ₅₀ 113 mg/L (48 hr) NOEC ₅₀ 9.4 mg/L (48 hr)	Appendix B-5
Acute Toxicity to Rainbow Trout (<i>Onocorhynchus mykiss</i>)	LC ₅₀ > 100 mg/L (96 hr) NOEC > 100 mg/L (96 hr)	Appendix B-6

1. Appendices referred to are contain in the full confidential EA for this product.

APPENDIX B-1

**SWISS GOVERNMENT CERTIFICATION OF COMPLIANCE FOR
PRODUCTION OF DIHYDROERGOTAMINE MESYLATE
AT SANDOZ, BASEL, SWITZERLAND**



ENVIRONMENTAL PROTECTION CERTIFICATE

1. The company SANDOZ PHARMA LTD operates facilities for chemical and pharmaceutical manufacturing at the following address:

SANDOZ PHARMA LTD
Lichtstrasse 35
CH-4002 Basel
Switzerland

2. These production facilities may only operate in accordance with permits issued by the responsible Authorities. In the permits 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 permits also cover the preparation of the Active Substance

Dihydroergotamine-mesylate

4. All buildings and plants of the company SANDOZ PHARMA LTD 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 periodic inspections.
6. It can here be stated that the undersigned Governmental Office has proved the correct building and producing permits are given.

Basel, 27. Juni 1994

SAUDEPARTEMENT BASEL-STADT
Der Departementssekretär


Dr. G. Vlecher

APPENDIX B-2

**SANDOZ PHARMA STATEMENT OF COMPLIANCE FOR PRODUCTION
OF DIHYDROERGOTAMINE MESYLATE AT SANDOZ, BASEL,
SWITZERLAND**

TO WHOM IT MAY CONCERN

TE. 06 32 111
TELEGR SANDOPHARM BASEL
TELEX 96 50 50 11
TELEFAX

3310/Ht/Ta

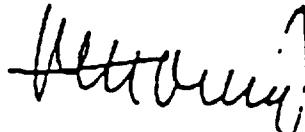
December 4, 1990

**STATEMENT RELATIVE TO ENVIRONMENTAL IMPACT OF THE MANUFACTURE OF THE DRUG
SUBSTANCE, DIHYDROERGOTAMINE MESYLATE**

We certify that:

The manufacture of the Drug Substance, Dihydroergotamine Mesylate, in the facilities of SANDOZ PHARMA Ltd., located in Basle, Switzerland, is performed in compliance with pertinent environmental control regulations established by the Swiss Federal Government.

SANDOZ PHARMA Ltd.


Dr. M. Horvath


Dr. M. Honermuth

APPENDIX C

**ENVIRONMENTAL SETTING OF SANDOZ PHARMACEUTICALS, EAST
HANOVER, NEW JERSEY**

ENVIRONMENTAL SETTING

Sandoz Pharmaceuticals Corporation (Sandoz) is located 22 miles west of New York City in East Hanover Township, Morris County, New Jersey. Approximately 1600 permanent and 400 temporary and contractor personnel are employed in this administrative, research and development, and production facility. East Hanover Township currently has a population of approximately 10,000.

The land surrounding the 185-acre Sandoz property is used for commercial and industrial complexes and residential development. The property is situated south of Route 10. A number of other commercial and industrial complexes are also located along Route 10. Directly south of the site there is a residential development which is separated from the site by an area of deciduous woodland. The western edge of the property is bounded by Black Brook and Ridgedale Avenue. West of Black Brook is an area of undeveloped, non-forested wetland. The eastern edge of the property is bounded by a deciduous woodland.

There are three areas of wetlands on the site, totalling 12.8 acres. Adjacent to Black Brook, on the property spur which extends from the southwestern corner of the site, there are 5.4 acres of non-forested wetland. A 5.9 acre area of forested wetland is located in the wooded area, near the center of the site. In the southwest corner of the site, there is a second area of forested wetland consisting of 1.5 acres.

There are several areas of deciduous woodlands on the Sandoz property. The total area of woodlands on-site is approximately 35 acres.

The developed portion of the site includes a number of buildings of various sizes, parking areas, roadways and large open, grassy areas. Buildings on the site cover an area of approximately 12 acres. Paved surfaces including parking areas and roadways account for approximately 28 acres of the site. The remainder of the property is open area that has been landscaped with grass and trees. This area covers approximately 100 acres. Uses of the property have changed over time. In the early 1900's, until 1947, a portion of the property was used as a dairy farm.

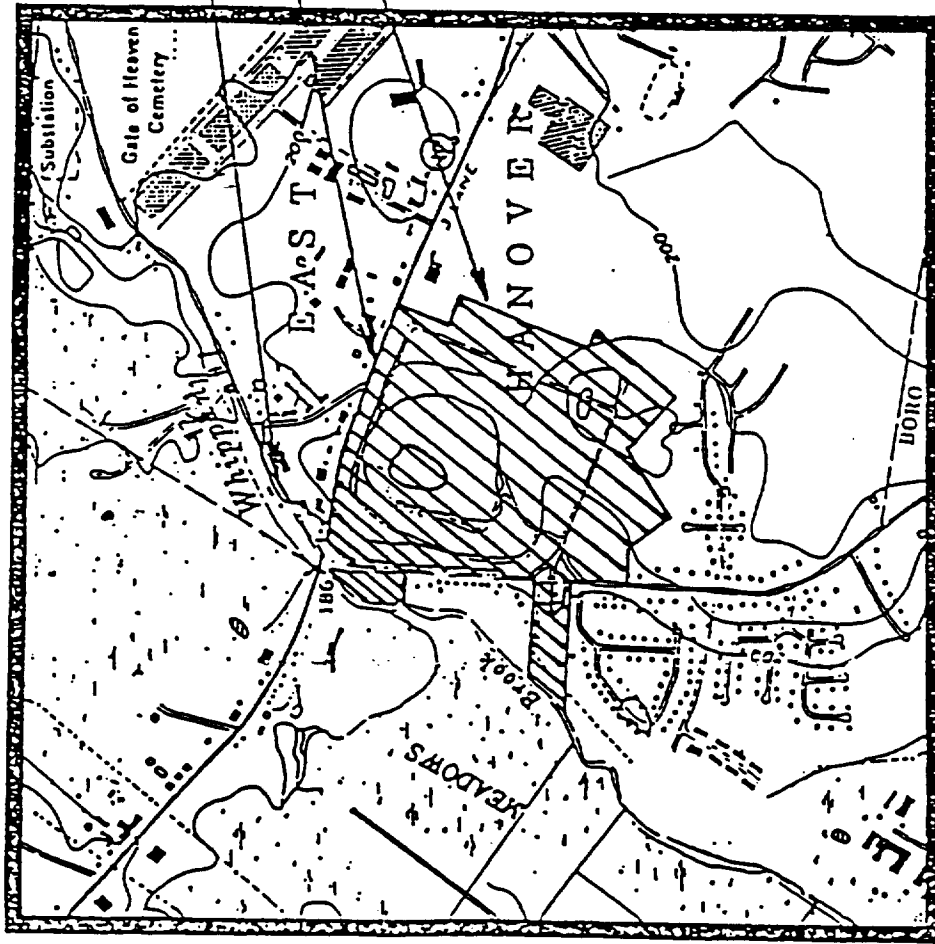
The climate in Morris County is humid and temperate with little influence from the ocean. The temperature in summer seldom exceeds 100°F and in winter is generally not below 10°F for long periods. Average annual precipitations range from 46 to 49 inches with the heaviest rainfall in July and August.

Surface water from the site drains to four storm water outfalls. At the eastern edge of the site, storm water discharges to state drainage ditches which drain to Pinch Brook. Pinch Brook is located approximately 1500 feet east of the site and flows south and then west to Black Brook. On the western edge of the property two discharge points drain to Black Brook. One storm water outfall is piped north from the site under Route 10 to the Whippany River.

There is a small area along Black Brook (elevations lower than 182 ft. m.s.l.) that is prone to flooding. The developed and operational area of the Sandoz property is on a hill well above the flood plain, therefore the site is not subject to flooding.

The soils underlying the Sandoz facility are of glacial origin. Subsurface investigations indicate that there is a layer of glacial till ranging from 20-60 feet thick beneath the site. Glacial till is typically a heterogeneous mixture of silt, clay, sand and gravel. Beneath the layer of glacial till is a layer of stratified drift. This deposit consists of sands and gravels. Bedrock is beneath the stratified drift layer and is described as "The Boonton Formation of the Brunswick Group" which typically consists of siltstone and sandstone.

The water table (first water) is present in the glacial till. This material typically has very low permeability. Groundwater is also present in the stratified drift. An unsaturated zone in the stratified drift separates groundwater in the glacial till from that in the stratified drift. Five production wells on the Sandoz property are screened in the stratified drift. Groundwater is also present in the underlying bedrock in joints and fractures and in separations along bedding planes.



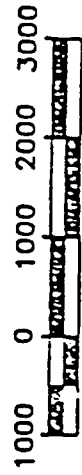
SOURCE: USGS 7.5 MINUTE QUADRANGLE
FOR MORRISTOWN, N.J. DATED
1954, AND PHOTOREVISED 1981.

SANDOZ, INC.
EAST HANOVER, NEW JERSEY

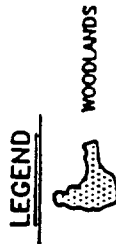
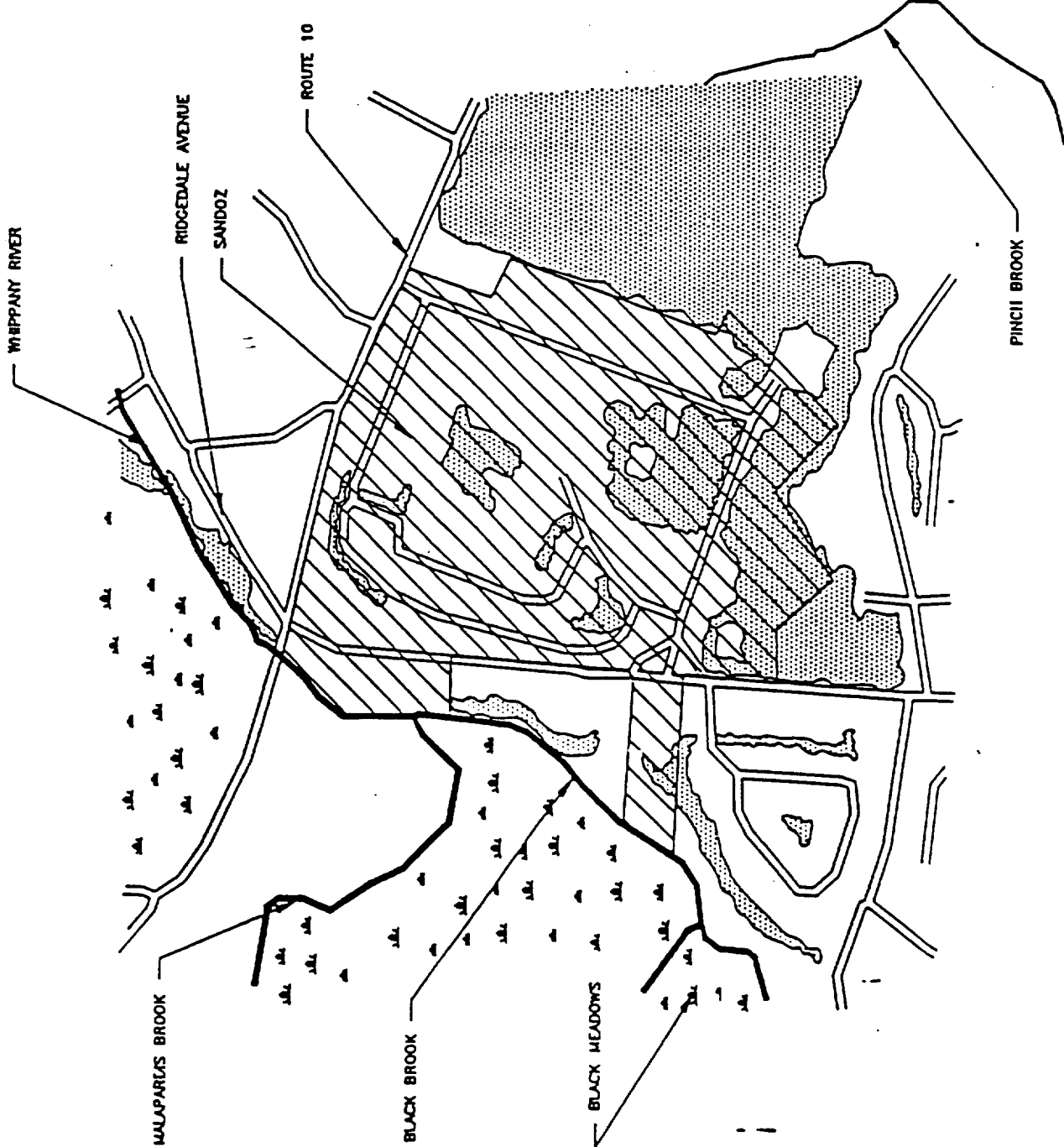
SITE LOCATION MAP

FIGURE No.	GEO FILE No.	DATE	REV.
1	90369	2/91	Ø

GEOEngineering
DOVER, N.J.
(201) 361-3800

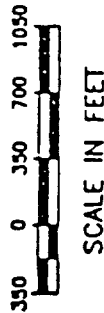


SCALE IN FEET



NOTES:

1. BASE PLAN TAKEN FROM MORRISTOWN QUADRANGLE, U.S.G.S. 1:50,000 SCALE, SERIES "C.A.D." ILLUSTRATION BY AMERICO, DIGITAL CARTOGRAPHY, AUSTON, VA, DATED 1/8/90.
2. WOODLANDS TAKEN FROM AN AERIAL PHOTOGRAPH DATED 2/90, SUPPLIED BY SANDOZ, LOCATIONS APPROXIMATE.



SANDOZ, INC. EAST HANOVER, NEW JERSEY		
AREA-WIDE PLAN		
FIGURE No.	GEO FILE No.	DATE
2	90369	FEBRUARY 1991
GEO Engineering		REV.
		Ø
		DOCK #1 0011341-3800

APPENDIX D

CURRENT NEW JERSEY AIR QUALITY PERMITS

Current New Jersey Air Quality Permits

Sandoz Pharmaceuticals Corporation
East Hanover, New Jersey
Building 415

PERMIT NO.	DESCRIPTION	STATUS*
113172	B415-SK-62	Temporary
113168	B415-DC-3	Temporary
113169	B415-DC-4	Temporary
113170	B415-DC-2	Temporary
113171	B415-DC-1	Temporary
107291	Lydon Dryer	Temporary
108323	S-5 FBD	Temporary
106630	PKII Blender Sifter	Temporary
106798	Film Coater Dust Collector	Temporary
107434	Devine Dryer	Temporary
107435	T-8 FBD	Temporary
113962	Steam Kettle-Room 48	Temporary

* Extensions are automatically granted for each permit every 90 days pending approval of permit applications.

APPENDIX E
WASTEWATER PERMITS

SIU PERMIT SUMMARY TABLE

COMPANY : Sandoz Pharmaceuticals - LAT: 40 50' 04"
 LOCATION: Route # 10 LONG: 74 26' 42"
 East Hanover Township
 Morris County INDUSTRY TOTAL FLOW: 0.150 MGD
 RECEIVING POTW: Parsippany-Troy Hills POTW NJPDES: NJ0024651
 REVIEW ENGINEER: Ali Chaudhry POTW DESIGN CAPACITY: 16 MGD

<u>PARAMETER</u>	<u>APPLICATION</u>	<u>PTSU LIMITATIONS</u>	<u>PERMIT LIMITATIONS</u>
All units in ug/l, unless specified			
		Maximum influent concentrations	Monthly Average Daily Max.
FLOW (MGD)	0.150	N/L	Monitor 0.150
BOD5, mg/l	134.5	300	Monitor 300
COD, mg/l	160	N/L	Monitor Monitor
TSS, mg/l	46	350	Monitor 350
OIL & GREASE, mg/l	40	100	Monitor 100
pH in S.U.	8.2	5.0 (min.)	9.0 (max.)
COPPER (TOTAL)	61.5	5,000	Monitor 5,000
LEAD (TOTAL)	8.2	5,000	Monitor 5,000
TNC (TOTAL)	84.7	5,000	Monitor 5,000
NO, mg/l *	170	N/L	Monitor 2.130
ALDRIN	0.42	N/L	Monitor ND (PRL 0.004)**
PCB - 1254	250	N/L	Monitor ND (PRL 0.5)**
CYANIDE	BMDL	1,000	Monitor 1,000

N/L: No numerical limit N/A: Not applicable
 mg/l: Milligrams per liter (ppm) ug/l: Micrograms per liter (ppb)
 BMDL: Below method detection limit as per 40 CFR 136.

* TIO means Total Toxic Organics which is a summation of all values greater than 10 micrograms per liter for the toxic organics listed in Table II of N.J.A.C. 7:14A - Appendix B. The concentration of all individuals toxic organics shall be reported.

** There shall be no discharge of Aldrin or Polychlorinated Biphenyl compounds. For the purpose of compliance monitoring, a permit reporting level (PRL) and corresponding EPA test method are specified. The permittee is required to analyze the wastewater according to the specified EPA test method 608. The permittee shall meet the permit reporting level for permit reporting purposes

Hanover Sewerage Authority

IPP PERMIT # 0-15

MONITORING AND DISCHARGE REQUIREMENTS: Sandoz Pharmaceutical

PARAMETER mg/L unless specified	PERMIT LIMIT Daily Maximum	SAMPLE TYPE	FREQUENCY OF SAMPLING	
			HSA	Industrial user
Temperature (°C)	43.3	Grab	12	6
pH (SU)	see attached	Grab	12	6
Biochemical Oxygen Demand (BOD)	220.0*	Composite** Grab	6 6	6
Suspended Solids	220.0*	Composite Grab	6 6	6
Nitrogen (Total)	40.0	Composite	6	6
Ammonia Nitrogen	***	Composite	6	6
Nitrate Nitrogen	***	Composite	6	6
Nitrite Nitrogen	***	Composite	6	6
Organic Nitrogen	***	Composite	6	6
Phosphorus (Total)	15.0	Composite	6	6
Cyanide (Total)	0.10	Grab	6	6
Arsenic (Total)	1.00	Composite	6	-
Barium (Total)	4.20	Composite	6	-
Cadmium (Total)	0.10	Composite	6	-
Chromium (Total)	3.00	Composite	6	-
Copper (Total)	3.00	Composite	6	-
Iron (Total)	5.00	Composite	6	6
Lead (Total)	0.50	Composite	6	6
Mercury (Total)	0.10	Composite	6	-
Nickel (Total)	1.00	Composite	6	-
Selenium (Total)	0.05	Composite	6	-
Silver (Total)	0.03	Composite	6	-
Zinc (Total)	3.00	Composite	6	-
Total Toxic Organics: (Priority Pollutant)				
Volatile Organics		Grab	12	6
Acid Extractables		Composite	6	6
Base Neutrals		Composite	6	6
PCB/Pesticides		Composite	1	1

APPENDIX F
CERTIFICATE OF COMPLIANCE

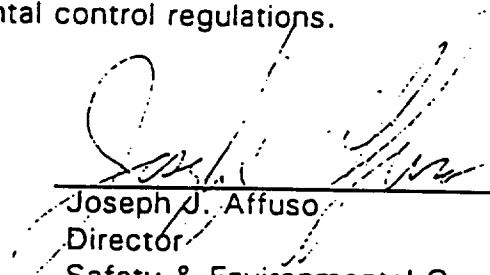
TEL. 201 503 7500
FAX 201 503 8265

July 7, 1994

To Whom It May Concern

I certify that:

The manufacture, control, handling, packaging and shipping of the new drug product MIGRANAL in the facilities of Sandoz Pharmaceuticals Corporation, located in East Hanover, New Jersey, are performed in compliance with pertinent federal, state, and local safety and environmental control regulations.



Joseph J. Affuso

Director

Safety & Environmental Operations

APPENDIX G

**MATERIAL SAFETY DATA SHEET FOR DIHYDROERGOTAMINE
MESYLATE**

Safety Data Sheet

 **SANDOZ**

Corresponding to EC Directive 91/155/EEC

Page: 1 / 5

3104932000000

Date of issue: 29.03.1994
Replaces version of: 24.03.1994

Trade name: DIHYDRO-ERGOTAMINE MESILATE

Product number: 3104932

1. Identification of the product and of the company

1.1 Product name:
DIHYDRO-ERGOTAMINE MESILATE

1.2 Company name:
SANDOZ PHARMA LTD
CH 4002 BASEL
PHONE : CH-061 324 11 11

1.3 Emergency phone number:
CH-061 324 33 33

2. Composition / information on ingredients

Chemical characterisation of the substance:
DIHYDRO-ERGOTAMINE MESILATE
Dihydro-ergot alkaloid
salt
CAS-Reg.No: 006190-39-2

3. Hazards identification

According to the present state of knowledge, provided that this product is handled correctly, there is no known danger to humans.

4. First aid measures

- 4.1 After contact with the eyes:
Immediately rinse eyes with running water and seek medical advice.
- 4.2 After contact with the skin:
After contact with skin, wash immediately with plenty of water and soap.
- 4.3 After inhalation:
Remove from danger zone. Obtain medical assistance.
- 4.4 After ingestion or accident:
If swallowed, wash mouth with plenty of water. Take patient to physician/factory medical centre or call for an ambulance.
Change contaminated clothes immediately. Rinse, and wash as usual.
- 4.5 Symptoms:
nausea
vomiting
feeling weak
- 4.6 Notes to physician:
antidopaminergic drugs, e.g. thiethylperazine, by physician

Safety Data Sheet

 **SANDOZ**

Corresponding to EC Directive 91/155/EEC

Page: 2 / 5

31049320000000

Date of issue: 29.03.1994
Replaces version of: 24.03.1994

Trade name: DIHYDRO-ERGOTAMINE MESILATE

Productnumber: 3104932

5. Fire fighting measures

5.1 Extinguishing media:

Suitable:
water
dry powder
foam

Not to be used:
no restrictions

5.2 Special advice in case of fire:

Cool container and metallic parts with a water spray jet
Set up threefold fire attack, use extinguishants singly or in combination, equip branchman and support team with complete protective apparatus.

Hazardous combustion gases:
carbon oxides
nitrogen oxides
sulfur oxides

6. Accidental release measures

6.1 After spillage, leakage, gas leakage:

Large amounts:
Call the fire-brigade immediately.
Evacuate endangered area, cut off area.
Must not be released into sewers, drains or wells.
Wear heavy protective equipment.
Take up in the dry state without forming dust. Consider Recycling

Small amounts:
Take up by mechanical means and dispose.
Put into lockable and properly labelled drums.

6.2 Cleaning of equipment:

Wash with plenty of water.

7. Handling and storage

7.1 Handling:

Measures to prevent fire and explosion:
Avoid formation of dust.
Observe the usual precautionary measures required for chemicals with dust explosive properties (Observe national regulations).
Keep away from sources of ignition.

7.2 Storage:

Technical protective measures:
Maximum storage temperature: 40 °C

Keep locked up.
Store container in cool and dry place.
Ensure efficient exhaust ventilation when using this product

Safety Data Sheet



Corresponding to EC Directive 91/155/EEC

Page: 3 / 5

51849320000000

Date of issue: 29.03.1994
Replaces version of: 24.03.1994

Trade name: DIHYDRO-ERGOTAMINE MESILATE

Product number: 3104932

8. Exposure controls and personal protection

8.1 Exposure controls:

8.2 Industrial hygiene:

8.3 Personal protective equipment:
Respiratory protection: mask, dust filter
Filter: DIN 3181 ABEK-P3
Eye protection: safety goggles
Hand protection: rubber gloves
Others: disposable suit

9. Physical and chemical properties

9.1 Form: powder

9.2 Colour: white slightly yellow

9.3 Odour: none

9.4 Change in physical state:

Melting point (°C): 220.0 - 240.0 (decomposing)
Boiling point: not applicable

9.5 Flash point: not applicable

9.6 Ignition temperature: no reaction up to 360 °C
Method: Sandoz Ignition test of deposited dust.

9.7 Explosion limits:

9.8 Density: not applicable

9.9 Vapour pressure: not applicable

9.10 Viscosity: not applicable

9.11 pH value:
(at 1.0 g/l H₂O): 4.4 - 5.4 at 20°C

9.12 Solubility in:

water	:	8.4	g/l at	20°C
ethyl alcohol abs.	:	4.3	g/l at	25°C
acetonitrile	:	10	g/l at	25°C

9.13 Partition coefficient n-octanol/water:

10. Stability and reactivity

Thermal decomposition:
Stable up to: 160 °C (Isoperibol, air open cup)
Reaction autocatalytic

Dangerous reactions:
Dust explosions are possible.

Safety Data Sheet

 **SANDOZ**

Corresponding to EC Directive 91/155/EEC

Page: 4 / 5

Date of issue: 29.03.1994
Replaces version of: 24.03.1994

Trade name: DIHYDRO-ERGOTAMINE MESILATE

Productnumber: 3104932

11. Toxicological information

LD50 acute oral: > 2000 mg/kg (rat)
LD50 acute oral: > 8000 mg/kg (mouse)

12. Ecological information

Biological elimination:
95 % (DOC - aerobic)
Method: OECD 301E * 1981 Mod. OECD screening test (ready)

Fish toxicity:
LC50 (96 h): > 100 mg/l
(rainbow trout (salmo gairdneri, oncorhynchus mykiss))
Method: OECD 203 * 1992 limit test

Daphnia toxicity:
EC50 (48 h): 113 mg/l
(daphnia magna (water flea))
Method: OECD 202 * 1984 acute tox.

Bacterial toxicity:
Respiration inhibition:
EC50 (3 h): > 100 mg/l
(activated sludge)
Method: OECD 209 * 1984 activated sludge. Respir. inhib.

13. Disposal considerations

Local regulations should be adhered to.

Incineration in controlled furnace.
May be deposited into a controlled land-fill; local regulations are binding.

14. Transport information

Regulations	Class	UN-Nr.	PGr.
RID/ADR:	not classified		
ICAO/IATA-DGR:	not classified		
GGVSee/IMDG-Code:	not classified		

15. Regulatory information

No labelling requirements according to EC Directives.

16. Other information

Safety data sheet in review

Main use: pharmaceutical active substance

039

179

Safety Data Sheet



Corresponding to EC Directive 91/155/EEC

Page: 5 / 5

5105932000000

Date of issue: 29.03.1994
Replaces version of: 24.03.1994

Trade name: DIHYDRO-ERGOTAMINE MESILATE

Productnumber: 3104932

Product should be stored, handled and used in accordance with good industrial hygiene practices and in conformity with legal regulations. The information contained herein is based on the present state of our knowledge and is intended to describe our products from the point of view of safety requirements. It should therefore not be construed as guaranteeing specific properties.

NDA 20,148

Submission Dates: 12/28/90

04/30/91

01/17/92

D.H.E. 45[®] Nasal Spray
Dihydroergotamine mesylate, USP
Sandoz Pharmaceutical Corp.
East Hanover, NJ 07936-1080

Reviewer: Kenneth W. Miller, Ph.D.

Type of Submission: Application for a New Dosage Form and Route of Administration

I. Synopsis:

Dihydroergotamine (DHE) mesylate, USP, is presently marketed (D.H.E. 45[®]) as a sterile solution for i.v. and i.m. injection for the treatment of migraine headache. The sponsor has also submitted a Supplemental NDA (5,929) for the purpose of adding the subcutaneous route of administration to the approved routes of administration of D.H.E. 45[®] Injection. The drug has very low oral bioavailability (<1%), due both to poor permeation across the gastrointestinal mucosa and a high presystemic clearance of the drug which is absorbed. The percentage of orally administered drug which reaches the systemic circulation as unchanged DHE and metabolite(s) has been estimated as only 30% of the administered dose. Oral DHE is not effective in aborting migraine attacks, but is marketed in several European countries as a migraine prophylactic (Dihydergot[®]).

The sponsor has proposed the nasal route of administration as way of increasing systemic availability as an alternative to parenteral administration. Drug absorption across the nasal mucosa is primarily via passive diffusion as in the gastrointestinal tract, but the blood draining the nasal mucosa returns directly to the right side of the heart without a "first pass" through the liver. Therefore, any DHE absorbed across the nasal mucosa should avoid the extensive "first pass effect" of the oral route. The nasal passages provide a highly vascularized structure with sufficient surface area ($\approx 180 \text{ cm}^2$) for absorption. Mucociliary clearance restricts drug contact time with the mucosa to 20-30 minutes, so compounds administered via this route must have reasonable cell membrane permeability.

The sponsor has submitted eight (8) biopharmaceutic/pharmacokinetic studies in support of the NDA. All of the studies were conducted in France during the early and mid-1980's on 99 healthy volunteers and 11 patients suffering from migraine headaches. Because of their European origin and time of completion, the documentation of the materials and methods, including the analytical assay procedure are not as complete as is desired at the present time. The human volunteer studies included 40 female subjects, who took birth control pills during the study period because of the known oxytocic effects of the ergot alkaloids. Unfortunately, the sponsor did not analyze for any gender associated difference in the drug's disposition in the original submission.

The analytical procedure used for all the studies was a _____ developed by J. Rosenthaler et al., of Sandoz. Although the assay appears reproducible and produces a straight

line log-logit standard curve, typical of an assay, the standards used to generate individual curves differed in number and concentration range among the studies, the precision and accuracy of the assay was judged "acceptable" with no definition of unacceptable. There was no differentiation between the Limit of Detection from the Limit of Quantitation and concentrations below the lowest standard were reported and used in pharmacokinetic calculations. No stability data was provided regarding the sample storage conditions (-18°C) prior to assay. Inasmuch as all of the studies were of crossover design and the individual study samples were analyzed in batches, the relative plasma concentration-time data were comparable. However, cross-study comparison of similar treatments exhibited some significant differences in Dose normalized AUC.

The proposed label recommends a 2 mg dose with instructions for the product as one spray (0.5 mg) per nostril, followed 15 minutes later by an additional spray per nostril. Although this protocol was used in the pivotal clinical trials, it was never used in a pharmacokinetic study protocol. In most pharmacokinetic protocols, the entire dose was either given as two sprays per nostril or one spray per nostril followed 10 minutes later by an additional spray per nostril.

Recommendation:

Despite some study deficiencies, including assay validation, the sponsor has provided sufficient information to characterize the pharmacokinetics of the nasal spray formulation of D.H.E. 45[®]. Therefore, this submission is acceptable provided the comments on pages 8-9 are adequately and promptly addressed by the sponsor.

The Pharmacokinetics and Metabolism subsection of the Clinical Pharmacology section of the proposed label is unacceptable. The section should be completely rewritten to include the basic pharmacokinetic parameters of the drug determined after i.v. or i.m. administration and the comparable parameters after intranasal administration. The stated relative bioavailability of 30-40% for the intranasal route of administration in the proposed label does not accurately reflect the large intersubject variability of this parameter, which could have clinical significance. There is no statement about the routes of metabolism, the possible P450 isozymes involved, or any statement about the drug's active metabolites. The value of 10 hours for the drug's $t_{1/2}$ is the mean from only two studies, and the value of 1.5 L/hr listed for total body clearance gives no indication of the considerable intersubject variability and there is no discussion of the significance of this high clearance.

**APPEARS THIS WAY
ON ORIGINAL**

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III. Background Information: The effectiveness of the ergot alkaloids in treating migraine headache was originally documented in the 1920's. DHE, the 9,10 dihydrogenated derivative of ergotamine, was introduced as iv therapy for migraine headache in 1946. Although highly effective in aborting migraine and ameliorating the symptoms of ongoing migraine, DHE has not been used as frequently as other ergots, because only parenteral formulations are marketed in the U.S. (i.v. or i.m.). The ergots, including DHE, appear to act by interacting with (stimulating) various serotonin receptors, particularly the 5-HT_{1D} receptor which also appears to be the main site of action for the anti-migraine drug, sumatriptan. DHE also interacts with several subclasses of adrenergic and dopaminergic receptors, which makes it a less selective CNS acting drug than sumatriptan. This may partially explain the difference in side effects between the two drugs, with nausea and vomiting a more common occurrence with DHE.

The exact mechanism of action of DHE as a migraine abortant is unknown, but it appears related to the drug's vasoconstrictor action in CNS arteriovenous anastomoses, which are postulated to open in a migraine attack, shunting blood from the capillary beds and producing local hypoxia and ischemia. DHE may also act to block the release of various neurotransmitters during migraine.

The intranasal route of drug administration has received considerable attention in the past decade, particularly for peptides and small proteins which are metabolized in the GI tract contents. The nasal mucosa is highly vascularized and drains directly into the venous circulation, bypassing the portal circulation to the liver and the first pass phenomenon. The nasal cavity has a volume of about 20 cm³, so a small volume of drug solution can be sprayed or instilled into the cavity which

is a mucus covered mixed cellular layer with a total surface area of about 180 cm². Drug diffusion across the nasal membrane is generally passive, with the rate and extent of diffusion a function of surface area, oil/water partition coefficient, extent of ionization, concentration of diffusant, and residence time or time in contact with the nasal mucosa.

Many of the nasal mucosal cells are ciliated. The cilia continually "sweep" the mucus layer toward the posterior of the nasal cavity where the mucus and trapped contents are swallowed. This "mucociliary clearance" controls contact time with the nasal mucosa to about 20-30 minutes. While the intranasal route of administration bypasses potential presystemic clearance by the GI mucosa and liver, the nasal cells do contain drug metabolizing ability (Phase I and II) along with peptidase and protease activities. The action of various chemical nasal absorption enhancers for peptides, may be in part due to their inhibitory action on nasal mucosal metabolism.

The intranasal route is an attractive mode of administration for DHE as the drug can be conveniently administered at the first sign of a migraine attack. Eventual efficacy of this route is dependent on consistent attainment of sufficient plasma concentrations with minimal local and systemic side effects.

A. Drug Formulation:

D.H.E. 45[®] contains ergotamine hydrogenated in the 9,10 position as the mesylate salt and is known as dihydroergotamine mesylate, USP. The proposed formulae for the nasal spray will be provided as a sterile solution in an amber glass ampul to distinguish it from the clear glass ampul of the Injection. The formula is as follows.

dihydroergotamine mesylate, USP	4.0 mg
caffeine, anhydrous USP	10.0 mg
dextrose, anhydrous USP	50.0 mg
carbon dioxide	qs
water for injection USP qs	1.0 ml

According to the sponsor, caffeine is added to enhance the solubility of the drug and act as a stabilizer. The recommended dose of DHE is 2.0 mg (4 sprays), which would deliver a dose of 5 mg of caffeine. Dextrose is added to make the solution isotonic. Accompanying the ampul is a spray device (Valois Vp3) which after priming (4 squeezes), delivers 120 mg ± 20% of the solution or approximately 0.5 mg of D.H.E. 45[®]. After breaking off the ampul top, the ampul is inserted into the spray device. Directions for patient use are to accompany the product. The dose is to be delivered as two puffs (one per nostril) followed by a repeat of two puffs 15 minutes later. The entire spray device and ampul are discarded after use.

B. Analytical Methods:

DHE plasma and urine levels are analyzed by

The assay procedure was

developed by Sandoz in the 1970's, and has been used with minor modifications for all studies submitted in this report. Because the studies were begun in the early 1980's, validation of the procedure was not as rigorous as that which is presently required for a NDA submission. Generally the deficiencies included only two usable quality control standards for determination of inter and intra study precision and accuracy, and a lack of a standard procedure for choosing the Limit of Quantitation of the assay.

Examination of all validation data submitted across studies, plus its universal use in non-Sandoz publications, supports the assay as acceptably accurate over the concentrations generated 0-13 hours post dose. However, concentrations reported 24 hours post dose were often below the value of the lowest standard, which had a C.V. of 40-50% (precision). Compared to the recent (1992) validation of the assay which was submitted in NDA Supplement 5929 (Study I-101), the reported 24 hour concentrations in the studies supporting this NDA were 20-25% of the Limit of Quantitation reported in Study I-101.

The use of concentrations lower than the lowest standard concentration for determination of $t_{1/2}$ may explain the wide interstudy variability of this parameter. With the exception of one study (#303-025), extrapolated AUC values were not used to compare different treatments, only trapezoidal AUC's. Approximately 75% of the AUC is generated by the doses used in the submitted studies in 8 hours following drug administration.

The results of the urinary excretion results of DHE were considered secondary by the reviewer and will not be discussed here. In every study urine kinetics were carried out in addition to plasma concentration studies, they corroborated the results from the plasma concentration data.

A copy of the Rosenthaler et.al., paper describing the assay is found in Appendix I.

IV. Summary of Bioavailability/Pharmacokinetics/Pharmacodynamics (Detailed Study Summaries are Provided in Appendix II)

A. Bioavailability/Bioequivalence

1. **Absolute Bioavailability: (Study #303-025).** Using all subjects data, $F = 43 \pm 24\%$ with a range of 13-101%. Excluding two outlier values of 78 and 101% bioavailability for the nasal spray respectively, the mean value for F is reduced to 34.2%. The sampling protocol did not include a concentration between 8 and 24 hours which reduced the confidence in the pharmacokinetic parameter estimates. AUC values used for bioavailability determination were obtained from fitting concentration-time data with a tri-exponential equations (ELSFIT), rather than trapezoidal rule, which was used in every other study.

2. **Relative bioavailability:** Studies (#303-002,-020,-021) compared the bioavailability of the intranasal preparation to an i.m. injection, the most common parenteral mode of administration of DHE. The relative bioavailability (F_{rel}) of the nasal spray was similar, $33.7 \pm 16.4\%$ and $31.3 \pm$

14.9%, for Study # -002 and -020, respectively. The range of F_{rel} for both studies was also similar, approximately 15-65%. Study #303-021 found a lower F_{rel} of $22 \pm 11.9\%$, with a range of 7.7-51.5%.

3. **Bioequivalence:** Although only one formulation of the nasal spray is proposed, the effect of several different variables on DHE absorption via the intranasal route were examined.

a. **Caffeine (Study #303-021).** The to-be-marketed formulation contains caffeine, purportedly added as a "solubilizing and stabilizing" agent. The mean relative bioavailability of [without/with] caffeine preparations was $104.7 \pm 51.9\%$. The AUC ratios of [without/with] ranged from 52-268%. The extent of variability seen between the two formulations was somewhat larger in this study, but large variability between administrations was seen in every study. There was no significant difference between the two formulations.

b. **Migraine attacks (Study #303-023).** During a migraine attack, many patients suffer various vasomotor symptoms including runny nose and stuffiness. There was no difference in the AUC's from equivalent doses during and between migraine attacks in chronic migraine patients. The protocol differed from suggested use in that the subjects waited for the symptoms of their migraine to develop before administration. The suggested use is to give the drug at the first sign of symptoms of an attack. Also, the dose was administered at one time rather than giving 1/2 the dose followed 15 minutes later by the second 1/2.

c. **Topical local vasoconstrictor (Study #303-024).** Fenoxazoline, a local vasoconstrictor, applied 10 minutes prior to the nasal administration of DHE produced a mean decrease in C_{max} and AUC of 27% and 15%, respectively. The administered dose of fenoxazoline was twice the recommended dose, so the clinical significance of the statistically significant reduction in DHE availability is questionable, and may be

d. **Mode of Administration (Study #303-110).** The time between the initial and second dose was examined. One treatment consisted of one spray in each nostril followed by one puff per nostril 10 minutes later. The second treatment separated the repeat doses by one puff 30 minutes later and a second single puff 60 minutes later after the initial two puffs. The relative bioavailability of the second treatment was 113% of the first treatment, but the first treatment (10 minute difference) produced a higher C_{max} .

4. **Food Effect.** All studies were performed in fasted patients. It is doubtful whether food would have an effect on nasal absorption.

B. Pharmacokinetics:

The results both within and between pharmacokinetic studies following intranasal administration

reveals that intersubject variability of the parameters is considerable (Table 1). There is almost a two-fold difference between the highest (-023) and lowest (-021) mean values for AUC and C_{max} . When these values were corrected for the actual dose delivered, there was no significant change in their relative values or variability.

Table 1. Cross-Study Comparison of AUC₀₋₂₄ and C_{max} after a 2 mg intranasal dose.

Study #	AUC (ng hr ml ⁻¹)	C _{max} (ng ml ⁻¹)
303-021	4.40 ± 1.95	0.98 ± 0.47
303-022	5.27 ± 2.92	1.13 ± 0.50
303-023*	7.82 ± 3.58	1.63 ± 1.05
303-024	6.11 ± 1.77	1.27 ± 0.42
303-110	6.70 ± 1.03	1.31 ± 0.27

*Only study which used migraine patients. All other studies in healthy volunteers.

Interestingly, the highest AUC and C_{max} values and variability of those parameters were obtained in the migraine patients, undergoing a migraine attack. There may be a need for patient education in the use of the spray device to ensure maximum efficiency of delivery to ensure the method of administration is not discarded for lack of clinical efficacy.

C. Metabolism:

Four metabolites of DHE have been isolated in humans. The main metabolite is 8' β -hydroxy-dihydroergotamine (8'-OH DHE), which is further metabolized by an opening of the proline ring. The other two metabolites are dihydrolysergic acid and dihydrolysergic acid amide. The 8'-OH DHE is also the primary metabolite formed in *in vitro* human microsome incubations. The 8'-OH metabolite appears equipotent with DHE in binding to six different monoaminergic binding sites including 5-HT and is equipotent to DHE in its venous vasoconstrictor activity in a number of animal models and man. The 8'-OH metabolite, which is produced in greatest concentration after oral administration of DHE, is probably responsible for the pharmacologic effects exhibited by oral DHE, which has an oral bioavailability of approximately 1%. Concentrations of this metabolite are much lower after i.m. and intranasal administration, because both routes of administration bypass the hepatic first pass effect (Study # 303-002). DHE metabolism is inhibited by macrolide antibiotics, with signs of ergot poisoning seen when macrolides and DHE are given together. No information on the specific pathway(s) inhibited by the macrolides has been provided by the sponsor. The nasal mucosa does contain drug metabolizing enzymes and peptidases, and the large intersubject variability in F_{rel} could be partially explained differences in the extent of nasal mucosa metabolism.

The major pathway of elimination of DHE and metabolites is via the bile with eventual elimination

in the feces. The renal clearance of the unchanged drug, is only 6-9% of the total systemic clearance. The drug is contraindicated in renal failure and hepatic disease patients.

D. Dose Proportionality:

Linear increases in C_{max} and AUC_{0-24} over the intranasal dose range of 1-4 mg (Study #303-022). There was a small decrease in the dose normalized parameters at the highest dose, but this could be due to volume of spray introduced into each nostril with resultant leakage from the site of absorption. There was considerable intersubject variability in both parameters, but with only several exception, both parameters increased linearly in each subject with increasing dose.

E. Subpopulation Analysis:

There was no indication of race or ethnicity in protocol. A reasonable number of female volunteers and patients participated in the pharmacokinetic studies, but no gender analysis was performed by the sponsor.

F. PK/PD relationships:

Because almost every study was done with healthy volunteers, and several studies utilized subtherapeutic intranasal doses (1 mg), there was little opportunity for PD analysis. In the dose proportionality study (#303-022), the side effect of nausea was only observed (4/15) at the highest dose (4 mg). Nasal stuffiness was reported as a side effect in every study.

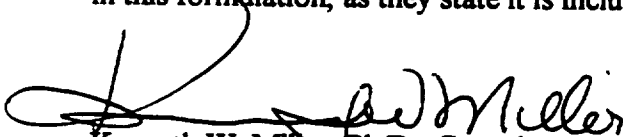
V. Comments(for FDA file).

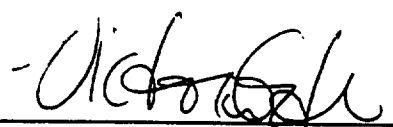
1. Because the pharmacokinetic studies were all conducted before 1987, the assay validation descriptions were not as rigorous as presently required. The use of concentrations lower than the lowest standard for the calculation of pharmacokinetic parameters was not uncommon and is unacceptable. Interestingly, the sponsor did not attempt to determine the terminal $t_{1/2}$ of DHE following intranasal administration except for the absolute bioavailability study (#303-025), where the sampling protocol was the most deficient.
2. The sponsor did not provide an analysis of age/gender/race on DHE disposition after intranasal administration.
3. Sponsor's description of DHE pharmacokinetics in the Clinical Pharmacology Section of the label is incomplete and inconsistent with other D.H.E. 45® product labels.
4. Sponsor did not provide labeling with a detailed instruction for use section.
5. Half-life discrepancies among studies submitted in this NDA and Study I-101 submitted in NDA 5,929 may be due to use of concentrations lower than lowest standard concentration in the

studies submitted in support of this NDA.

VI. Labeling Comments:(Send to Sponsor)

1. Sponsor is supplying detailed directions for loading the spray device, but does not describe the proper technique for using the spray device, including depth of insertion of device into nostril, head position and inhalation technique, if any. Improper and inconsistent administration technique could have contributed to the large inter and intra subject variability in absorption of DHE after intranasal administration.
2. The Clinical Pharmacology section of the label and those of other D.H.E. products have to be rewritten to make them consistent. The absorption of DHE after intranasal administration is quite variable, yet this is not conveyed in the label. The fact that DHE "constitutes 70-80% of concentration of drug-related materials", does not mean a relatively low degree of metabolism of DHE after intranasal administration. The statement about urinary recovery after intranasal administration being about 2% is not very useful. Renal Clearance and Systemic Clearance values, plus their extent of variability is more useful. The sponsor seems to choose $t_{1/2}$ values for this drug using a random selection process.
3. The sponsor is requested to provide an analysis of DHE pharmacokinetics as a function of age, race and gender. A portion of this information may be obtained from the literature.
4. Healthy female volunteers who participated in studies took anovulatory drugs. The sponsor is requested to provide information regarding the effect of anovulatory steroid hormones on DHE pharmacokinetics, and to state conclusions in labeling.
5. Sponsor should discuss with Agency the potential need for another study examining the effect of nasal decongestants (vasoconstrictors) on DHE bioavailability inasmuch as the dose of fenoxazoline used in Study #303-024 was double that normally recommended.
6. Sponsor is not permitted to advertise or otherwise make claims regarding the caffeine present in this formulation, as they state it is included only as a "solubilizing and stabilizing" agent.


Kenneth W. Miller, Ph.D., Consultant
Supervising Pharmacokineticist, Victoria Hale, Ph.D.

 3/16/94

cc: NDA 20,148
HFD-019 (FOI)
HFD-426: Miller, Hale, Fleischer, chron, drug, reviewer, novel dosage form
HFD-120: 3 copies
HFD-340: Viswanathan

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ATTACHMENT I

5 pages

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ATTACHMENT II

Study # 303-002
(Volume 8, p. 06-00576)

Title: Study Comparing Bioavailability by the Nasal and Intramuscular Routes of Administration.

Objective: To compare the relative bioavailability of nasally administered DHE to that of the i.m. route of administration.

Site: Sandoz Pharmacokinetics Research Centre, Rueil-Malmaison, France. Conducted in 1982.

Study Design: Randomized, double blind two-way crossover. All subjects received both injection and nasal spray. Placebo i.m. injection and nasal spray given with alternate therapy.

Subjects: Ten (10) healthy volunteers. Smoking history unknown.

Demographics: 5 females, 5 males, ages 20-39, mean = 25.8 yrs, weight 45-65, mean = 56.6 kg.

Formulations: Injection solution, batch # 30 containing 1 mg/ml DHE mesylate. Nasal Spray solution, batch # G 937, containing 4 mg/ml DHE mesylate. No direct mention of other constituents. Caffeine was not included in placebo nasal spray.

Dosing: No information as to location of i.m. injection or the method of administration of the nasal spray. A dose of 1 mg was given by both routes of administration.

Adjunct Treatment. Female subjects took anovulatory drugs. Subjects were fasted overnight and subjects ate 10 minutes after drug administration. Subjects drank 100 ml water/hour for first 4 hrs post drug administration to ensure diuresis.

Sampling Protocol: Twelve blood samples including blank, 10', 20', 40', 60', 2 hrs, 3 hrs, 4 hrs, 6 hrs, 8 hrs, 11 hrs, and 24 hrs. Urine collected for 72 hours. A blank urine plus 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hrs.

Assay: DHE in plasma and urine were analyzed by developed by J. Rosenthaler.

Data Analysis: C_{max} , T_{max} , AUC_{0-24} (trapezoidal rule), $Ae_{(0-72)}$ plus several other urinary excretion parameters. Relative bioavailability determined by ratios of AUC's and Ae's. No correction made for actual dose given, assumed 1 mg was delivered.

Conclusion: Relative bioavailability of the intranasal to i.m. route was $33.7 \pm 16.44\%$ (mean \pm S.D.) with a range of 16.7-65.5%. Similar results were obtained using urine data. Approximately 6% of the i.m. dose was recovered unchanged in the urine. The interindividual variability was much smaller in this study, 14.5 and 4.8% C.V. for nasal and i.m. routes of administration. The reason for this is not known, but sponsor has been asked to comment.

Study # 303-020
(Volume 7, p. 06-00282)

Title: Single Dose Comparative Bioavailability Study with DHE Nasal Spray versus DHE LM. in Healthy Volunteers.

Objective: To compare the relative bioavailability of nasally administered DHE to the commonly used intramuscular injection mode of administration.

Site: Completed in 1985

Study Design: Randomized, open, two-way crossover.

Subjects: Eighteen (18) healthy volunteers. Smoking history unknown.

Demographics: 8 females, 10 males, ages 19-31, mean = 23.9 yrs, weight: 49-80, mean = 63.8 kg.

Formulations: DHE for injection, containing 1 mg/ml, KNGL 15642-33, Batch # 51. Solution for DHE nasal spray (4 mg/ml) containing caffeine and dextrose, batch # 70479. Spray device delivers 0.120 ml per puff (0.480 mg/puff).

Dosing: Treatment A is 1 ml of DHE injection solution administered i.m. into superolateral area of buttocks. Treatment B is 1 mg (2 puffs), one into each nostril. The exact dose administered was determined by pre and post weighing of the dosing device.

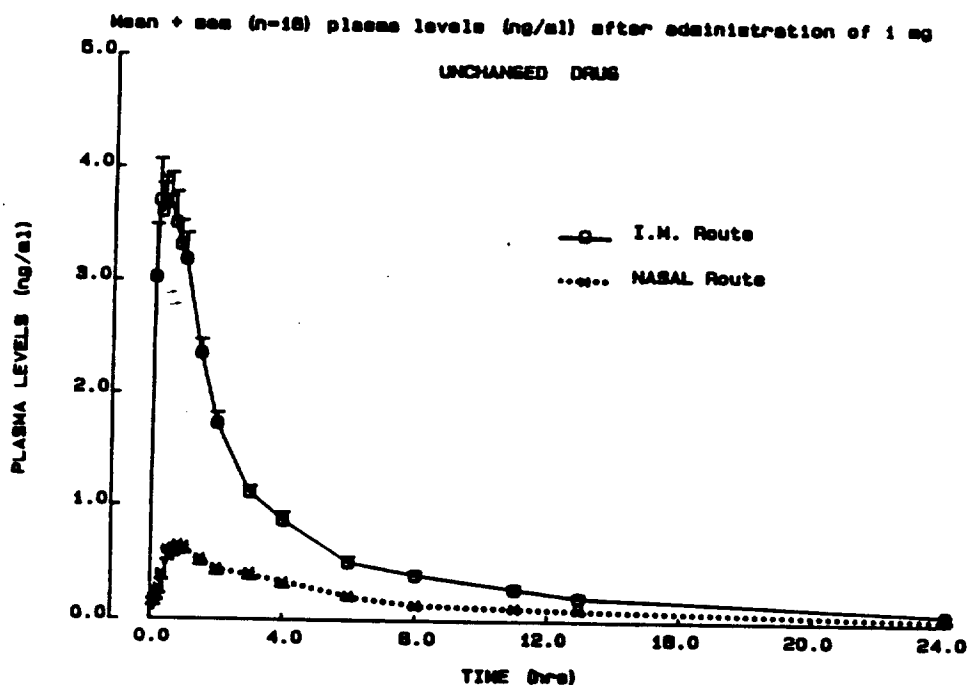
Adjunct Treatment: Female subjects took birth control pills. Subjects fasted prior to administration and for 1 hour post dosing. Subjects required to drink 100 ml of water every hour for 4 hours post dose to ensure diuresis.

Sampling Protocol: 18 blood samples including blank, 5', 10', 15', 20', 30', 40', 50', 60', 90', 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 11 hr, 13 hr, and 24 hr. Urine collected for 72 hours. A blank urine plus 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, 48-60 and 60-72 hrs.

Assay: DHE in plasma and urine was analyzed by developed by J. Rosenthaler, Sandoz.

Data Analysis: Parameters T_{max} and C_{max} obtained directly from data. AUC_{0-24} calculated using linear trapezoidal rule. A_e (0-72) was expressed as 5 dose administered. Data were also fit with PHARM program. Several models were needed to "best fit" individual data including, first order absorption followed by biexponential disposition, zero order absorption and biexponential disposition, and first order absorption and elimination. AUC_{0-} was calculated by adding terminal phase area, C_{min}/β , to trapezoidal area and by integrating exponential expression. Relative bioavailability calculated both with correction for actual dose delivered or assumption of 1 mg delivered by nasal administration.

Conclusion: Considerable variability in relative bioavailability of nasally administered drug. Without correction, $F_{rel} = 31.3 \pm 14.85\%$ (mean \pm S.D.); range = 9.5-67.3, and with correction, $F_{rel} = 38.4 \pm 16.12\%$; range = 15.1-68.7. The interindividual C.V. for AUC and C_{max} were approximately 40% after nasal administration vs. 25% after i.m. administration. Other PK parameters were determined for the i.m. injected drug including an Apparent Clearance = 1212 ml min^{-1} , an apparent Volume of Distribution = 11.9 l kg^{-1} and a Renal Clearance of approximately 90 ml min^{-1} . The $t_{1/2}$ of DHE from this study is approximately 7.5 hours. These results are consistent with extensive presystemic clearance of orally administered DHE and also minor contribution of renal route of elimination.



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Study # 303-021
(Volume 10, p. 06-01327)

Title: Comparative Bioavailability of Single Dose of DHE Nasal Spray With or Without Caffeine in Healthy Volunteers.

Objective: To determine the relative bioavailability of two formulations of the DHE Nasal Spray to an i.m. injection of DHE. The formulations differed in the presence or absence of 1% caffeine.

Site: July-August 1985.

Study Design: Randomized, open, three-way crossover.

Subjects: Eighteen (18) healthy volunteers. Smoking history unknown.

Demographics: 8 females, 10 males, ages: 19-31, mean = 22.6, weight: 50-97, mean = 65.7 kg.

Formulations: Injection (1 mg/ml) batch # 048; DHE Nasal Spray with Caffeine (4 mg/ml), batch # 70493; DHE Nasal Spray without caffeine (4 mg/ml), batch # G 278. Both Nasal Sprays contain 10% dextrose. Pulsadoz[®] Spray Device which delivers an average of 0.120 ml (0.480 mg) per puff used for both.

Dosing: I.M. injection (1 ml) administered into the superolateral area of the buttocks. After priming, both nasal sprays administered 2 mg DHE as four (4) puffs, two into each nostril. Although not stated in protocol, assume two puffs given consecutively in each nostril or all within one minute. The spray device was weighed after priming pre and post dose to determine actual dose delivered to nose.

Adjunct Treatment: Female subjects took birth control pills. Subjects fasted overnight and received breakfast one hours after drug administration. Subjects required to drink 100 ml water each hour for four hours post drug administration to ensure diuresis.

Sampling Protocol: 15 blood samples including blank, 5', 10', 15', 30', 45', 60', 90', 2 hrs, 3 hrs, 4 hrs, 6 hrs, 11 hrs, 13 hrs, and 24 hrs. Urine collected for 72 hours. A blank urine plus 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, 48-60 and 60-72 hours.

Assay: DHE in plasma and urine was analyzed by developed by J. Rosenthaler, Sandoz.

Data Analysis: T_{max} , C_{max} , AUC_{0-24} (trapezoidal rule), $Ae_{(0-72)}$, plus several other urinary excretion rate parameters. Relative bioavailability of each nasal spray formulation to i.m. injection and to each other was calculated from ratio of AUC's and $Ae_{(0-72)}$.

Conclusions: Relative bioavailability of nasal spray formulations was approximately 22 % using assumed nasal dose of 2 mg, and approximately 25% using actual dose administered, determined from weighing of spray device. This values for the relative bioavailability of the nasal spray are

lower than those from protocols 303-002 and 303-020 which were of the order of 33%. The two different nasal spray formulations appear to be bioequivalent. However, there was considerable variability in the results with relative bioavailability of the [without caffeine/with caffeine] AUC ratios varying from 52-268%. The mean of the individual relative bioavailability determinations of [without/with] caffeine formulations was $104.7 \pm 51.9\%$ when uncorrected data used and $105.9 \pm 50.5\%$ with corrected data. Comparison of the mean AUC's of the [without/with] caffeine formulations yields a figure of 92.5% relative bioavailability.

In the ANOVA analysis comparing the two nasal formulations, a significant period effect was found, which resulted in a 7.7% increase in the dose administered during the second nasal treatment. The sponsor attributes this to a learning effect with the Pulsadoz®.

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Study # 303-022
(Volume 8, p. 06-00672)

Title: Bioavailability of Increasing Single Dose DHE Nasal Spray in Healthy Volunteers.

Objective: To determine to AUC and C_{max} after administration of increasing doses (1,2 and 4 mg) of DHE nasal spray in healthy volunteers.

Site: Pharmacokinetics Research Centre; Sandoz Labs; Rueil-Malmaison, France. 1985-86.

Study Design: Random, open, three-way crossover.

Subjects: Fifteen (15) healthy volunteers. Nine smokers, six non-smokers.

Demographics: 8 females, 7 males, ages 22-33, mean = 26.4 yrs, weight:50-81, mean = 63.4 kg.

Formulation: DHE Nasal Spray (4 mg/ml) Batch # 70479. Pulsadose® Spray Device.

Dosing: 1 mg dose given as 1 puff into one nostril at T = 0, followed by 1 puff into other nostril at T = 10 minutes; 2 mg dose given as 1 puff into each nostril at T = 0, followed by 1 puff into each nostril at T = 10 minutes; 4 mg dose given as 2 puffs into each nostril at T = 0, followed by 2 puffs into each nostril from a new spray device at T = 10 minutes. Actual dose administered was determined by pre and post weighing of spray device after priming and use, respectively.

Adjunct Treatment: Female subjects took birth control pills. Subjects fasted prior to dose and were fed one hour after treatment. Other meals followed on schedule.

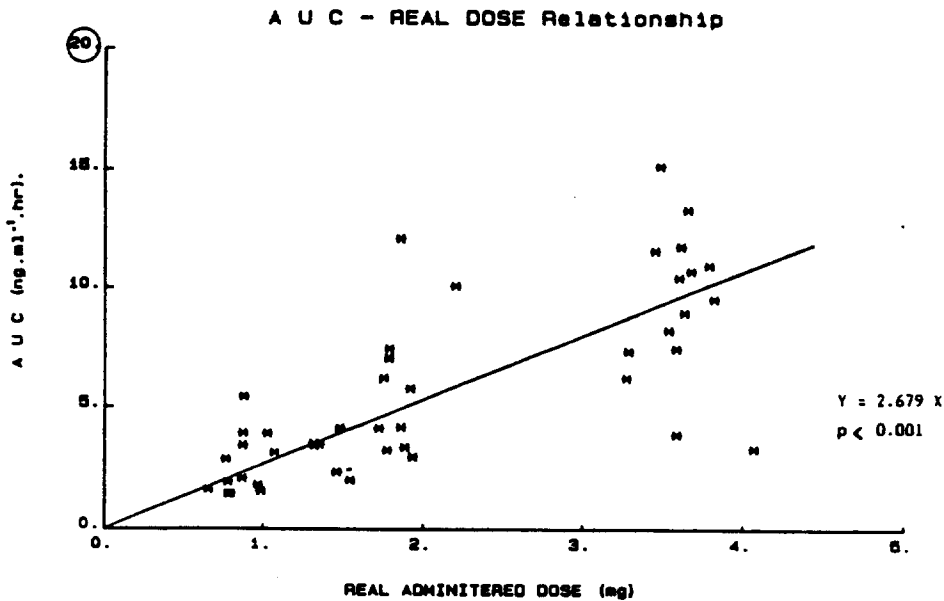
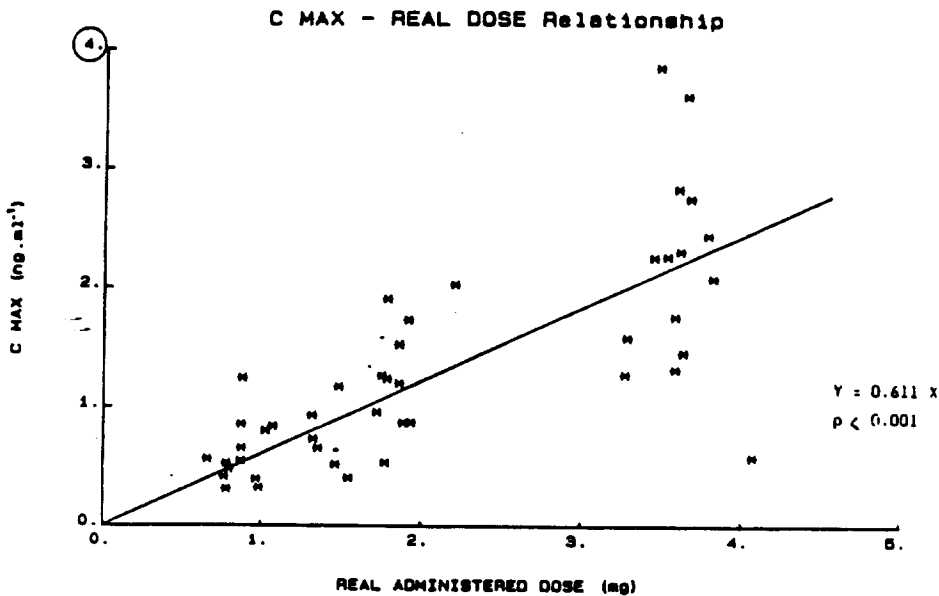
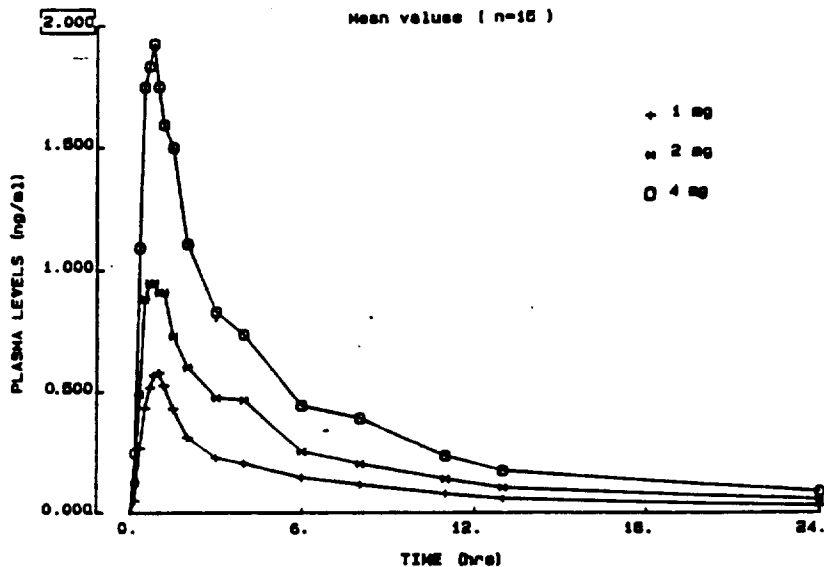
Sampling Protocol: 17 blood samples including blank, 10', 20', 30', 40', 50', 60', 70', 90', 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 11 hr, 13 hr and 24 hr. Urine collected for 72 hours. A blank urine plus 0-2, 2-4, 4-6, 6-8, 8-11, 11-24, 24-36, 36-48, 48-60, and 60-72 hrs.

Assay: DHE in plasma and urine was analyzed by . . . method developed by J. Rosenthaler, Sandoz.

Data Analysis: C_{max} , T_{max} and AUC_{0-24} (trapezoid rule) determined from plasma data. No analysis of urinary excretion data. Linear regression analysis with line passing through the origin was performed using both theoretical and actual doses administered.

Conclusions: The C_{max} and AUC_{0-24} increased in a linear manner with both theoretical and actual dose administered. However, there was a slight decrease in the dose normalized parameters at the highest dose, possibly due to leakage from the site of absorption . The C.V.'s for both C_{max} and AUC were of the order of 40-50% for the three doses. The plots of C_{max} and AUC vs Dose are attached. There was no significant change in T_{max} , but there was a slight shift to smaller values as the dose increased

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Study # 303-023
(Volume 8, p. 06-00886)

Title: Comparative Pharmacokinetics of DHE Nasal Spray During and in the Absence of Migraine Attack.

Objective: The vasomotor activity accompanying a migraine could affect the vasculature of the nasal mucosa. Whether the bioavailability of DHE administered by nasal spray would be different during a migraine headache as compared to a symptom free period was assessed.

Site: 1984-85.

Subjects: Eleven (11) patients completed the pharmacokinetic phase of the study. Patients suffered from 2-10, mean = 4.5, migraine attacks per month. DHE nasal spray was administered 2.25-72, mean = 12.83 hrs after beginning of attack.

Demographics: 6 females, 5 males, age; 45-56, mean = 49.7, weight; 50-85, mean = 64.1 kg.

Formulation: DHE Nasal Spray (4 mg/ml), Batch # 70479. Pulsadoz® Spray Device.

Dosing: Four puffs of nasal spray, two into each nostril. There was not interim period between puffs into the same nostril, as in other protocols. The theoretical dose = 2 mg. The first treatment was always during an attack and the second at least three days later when patient was symptom free.

Adjunct Treatments: No ergotamine containing preparations could be taken during the week preceding the migraine attack.

Sampling Protocol: 10 blood samples including bland, 15', 30', 45', 60', 90', 2.5 hrs, 4 hr, 8 hr, and 24 hrs. Urine samples were collected for 48 hours, in two 24 hour fractions.

Assay: DHE in plasma was analyzed by method developed by J. Rosenthaler, Sandoz. There was no report of urinary excretion of DHE.

Data Analysis: T_{max} , C_{max} and AUC_{0-24} (trapezoidal rule) were obtained. Relative bioavailability of the DHE nasal spray during an attack was compared to symptom free period was calculated from the ratios of the corresponding areas (0-24 hrs).

Conclusion: There was no difference in the AUC_{0-24} or the C_{max} when the drug was administered during a migraine attack or during a symptom free period. Unfortunately, the dosing protocol used in the study is not close to that suggested for clinical use of the product. The recommended use of the product is to use at the beginning of an attack to abort the headache. Also, the dose is to be given as one puff in each nostril, followed by one puff in each nostril 15 minutes later. Administering two puffs in the same nostril consecutively can lead to "leakage" from the nasal cavity. The variability of C_{max} and AUC among patients was quite large, with C.V. 50-60%.

Study # 303-024
(Volume 9, p. 01007)

Title: Influence of Concomitant Use of a Local Vasoconstrictor Upon the Bioavailability of DHE Nasal Spray in healthy Volunteers.

Objective: Assess the bioavailability of DHE Nasal Spray with and without prior use of the vasoconstrictor, fenoxazoline.

Site: Pharmacokinetic Research Centre, Sandoz Labs, and
Jan-May 1985 and September 1985.

Study Design: Used an unbalanced crossover design since seven of the subjects took part in protocol 303-110, and the administration of the vasoconstrictor formed the third arm of a three-way crossover. Remainder of subjects were randomized in two-way crossover.

Subjects: Eighteen (18) healthy volunteers.

Demographics: 8 females, 10 males, ages: 21-37, mean = 26.2 yrs, weight: 50-70, mean = 60.5 kg.

Formulations: DHE Nasal Spray (4 mg/ml), Batch # 70479. Pulsadoz® Spray Device which delivers 0.120 ml/puff (0.480 mg/puff). Fenoxazoline (1 mg/ml fenoxazoline hydrochloride), Batch # 5015 is marketed under the name Aturgyl® in France. Because of the extreme variability of the delivery of fenoxazoline using the marketed dispenser, drug was transferred to glass bottle and dispensed with sponsor's spray device. Dose delivered was 2x usually recommended dose.

Dosing: DHE Nasal Spray (2 mg) administered as one puff in each nostril at T= 0, followed by one puff in each nostril at T = 10 minutes. Fenoxazoline (0.21 mg) administered as one puff in each nostril, followed ten minutes later by the DHE Nasal Spray administered the same as above. The actual dose administered was determined by pre and post weighing of the spray device.

Adjunct Treatments: Female subjects took birth control pills. Subjects were fasted overnight and were administered breakfast one hour after drug administration. Subjects were required to drink 100 ml water/hour for four hours post dose to ensure diuresis.

Sampling Protocol: 17 blood samples including blank, 5', 10', 20', 30', 40', 60', 70', 90', 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 11 hr, 13 hr and 24 hr. Urine was collected for 72 hours. A blank urine plus 0-2, 2-4, 4-6, 6-8, 8-11, 11-24, 24-36, 36-48, 48-60 and 60-72 hours.

Assay: DHE in plasma and urine was analyzed by _____ developed by J. Rosenthaler, Sandoz.

Data Analysis: T_{max} , C_{max} , AUC_{0-24} (trapezoidal rule), $Ae_{(0-72)}$ were determined. Relative bioavailability calculated from the ratio of the corresponding AUC's and Ae 's.

Conclusions: Both C_{max} and AUC were reduced (27% and 15% respectively), when DHE was administered 10 minutes after fenoxazoline. The $Ae_{(0-72)}$ was reduced 9% after fenoxazoline. These reductions suggest that DHE Nasal Spray after fenoxazoline is not bioequivalent to that without pre administration of the vasoconstrictor. However, the clinical significance of the protocol is questionable as the dose of vasoconstrictor was 2x the usual dose. Furthermore, most migraine patients would not be inhaling a vasoconstrictor only 10 minutes before using the DHE Nasal Spray.

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Study # 303-025
(Volume 7, p. 06-00223)

Title: The Kinetic Study of the Bioavailability of DHE as a Nasal Spray: Nasal vs. I.V. Pharmacokinetics.

Objective: Absolute bioavailability study of DHE nasal spray in healthy volunteers.

**Site:
February-April 1986.**

Study Design: Randomized, open two-way crossover.

Subjects: Twelve (12) healthy male, medical student volunteers. All were non-smoking.

Demographics: Ages: 24-31, mean = 26.5 yrs, weight: 65-93 kg, mean = 75.2 kg.

Formulations: DHE injection, Dihydergot® (KNGL 15642.28, Batch # 002A3) of 1 mg/ml DHE mesylate. DHE nasal spray (KNGL 71187.01, Batch # I016 L4) containing 0.5 DHE mesylate/puff.

Dosing: For i.v. dosing, 1 ml (1 mg) was given as a bolus with volunteer lying down. For intranasal administration, 2 puffs of 0.5 mg given within 30 seconds of each other. Dose delivered was not determined by pre and post weighing of delivery device as in other studies.

Adjunct Treatments: No alcohol-containing beverages permitted 12 hours before and 48 hours after administration. Food/fasting state not defined. No concurrent medications allowed.

Sampling Protocol: Fourteen blood samples including blank, 5', 10', 20', 30', 45', 60', 2 hr, 3 hr, 4 hr, 6 hr, 24 hr, 36 hr and 48 hr.

Assay: DHE analyzed using _____ method of J. Rosenthaler, Sandoz. Attempt was made to also assay the _____ of DHE using _____ but most values were too low.

Data Analysis: Both the i.v. and intranasal data were fit using the Program ELSFIT. Initial parameter estimates were obtained with DISCRETE. Data for both modes of administration required 3 exponentials. With intranasal data, one exponential described absorption phase, and two exponentials the disposition phase. For the i.v. data, three exponentials were used to describe the disposition curve. The AUC's (0-∞) were calculated by integrating the fitted curves. The sponsor was requested to recalculate the AUC data from 0-24 hours using the trapezoidal rule so that the data from this study could be compared to the other bioavailability studies which used trapezoidal areas. The results of the two methods of data analysis are compared under Conclusions.

Conclusions: Using the data from all twelve subjects the absolute bioavailability of the nasal spray was $43 \pm 24\%$ with a range of 13-101%. Two of the subjects were "outliers" with values of 78 and 101% respectively. Eliminating these values, the absolute bioavailability is 34.2%. The sampling protocol was poorly designed with no samples between 8 and 24 hours. This may explain the long $t_{1/2}$ reported in this study (13.66 ± 4.6 hrs). Examination of the absolute values from the two "outlier" subjects suggests that the AUC following i.v. administration to Subject 7, who had a 101% bioavailable intranasal value, may have been incorrect in that the AUC is about 50% of the next lowest AUC following i.v. administration. The subject who exhibited the 78% bioavailable intranasal value had an AUC following i.v. which was relatively high. There is no reason to reject this value.

When the AUC's were recalculated using the trapezoidal rule, the intranasal/i.v. AUC ratios increased in every instance. Using all 12 subjects, the absolute bioavailability was $53 \pm 27\%$, with a range of 28-121%. Eliminating Subject 7, the absolute bioavailability is $47 \pm 17\%$, with a range of 28-80%. It should be noted that all the subjects used in this protocol were healthy male medical students, and all were non-smokers. Perhaps the fact that they were non-smokers played a role in the higher values for intranasal bioavailability seen in this protocol. The sponsor did note smoking status of volunteers in some of the protocols, but not all.

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Study # 303-110
(Volume 7, p. 06-00015)

Title: Influence of the Mode of Administration

Objective: To compare the effect of the timing between subsequent doses on relative bioavailability of nasally administered DHE.

Site: Pharmacokinetics Research Centre; Sandoz Labs; Rueil-Malmaison, France, July 1985.

Study Design: Randomized, open, two-way crossover.

Subjects: Eight (8) healthy volunteers, Smoking history is unknown..

Demographics: 3 females, 5 males, ages: 22-37, mean = 27.6 yrs, weight: 55-70 kg, mean = 62.5

Formulation(s): DHE Nasal Spray (4 mg/ml), Batch # 70479. Pulsadoz[®] Spray Device, Batch 84.04.11 which delivers 0.120 ml per puff (0.480 mg/puff).

Dosing: Treatment A: Administration of one puff in each nostril at T=0, plus one puff in each nostril after 10 minutes elapsed, T=10. Treatment B: Administration of one puff in each nostril at T=0, plus one puff in one nostril after 30 minutes, T=30, plus one puff in other nostril after 60 minutes, T=60. Actual dose administered was determined by pre and post weighing of spray device after priming.

Adjunct Treatments: Female subjects took anovulatory drugs. Subjects were fasted overnight prior to drug administration and ate one hour post administration. Required to drink 100 ml/hr of water for four hours post dose to ensure diuresis.

Sampling Protocol: 17 blood samples including blank, 5', 10', 20', 30', 40', 60', 70', 90', 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 11 hr, 13 hr, 24 hr. Urine samples for 72 hrs. A blank urine plus 0-2, 2-4, 4-6, 6-8, 8-11, 11-24, 24-36, 36-48, 48-60, 60-72 hrs.

Assay: DHE in plasma and urine was analyzed by developed by J. Rosenthaler, Sandoz. This assay used for all DHE pharmacokinetic studies.

Data Analysis: C_{max} , T_{max} , AUC_{0-24} , $Ae_{(0-72)}$ plus several other urinary excretion parameters. Relative bioavailability calculated from ratio of AUC's (not log transformed) and ratio of Ae's (0-72).

Conclusions: Relative bioavailability of Treatment B = 113% of Treatment A. Treatment A had higher C_{max} . Label recommends modified Treatment A with 15 minutes between puffs. Approximately 2-3% of administered dose appears unchanged in urine.

ATTACHMENT IV

STUDY # 303-002

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FIG. 1

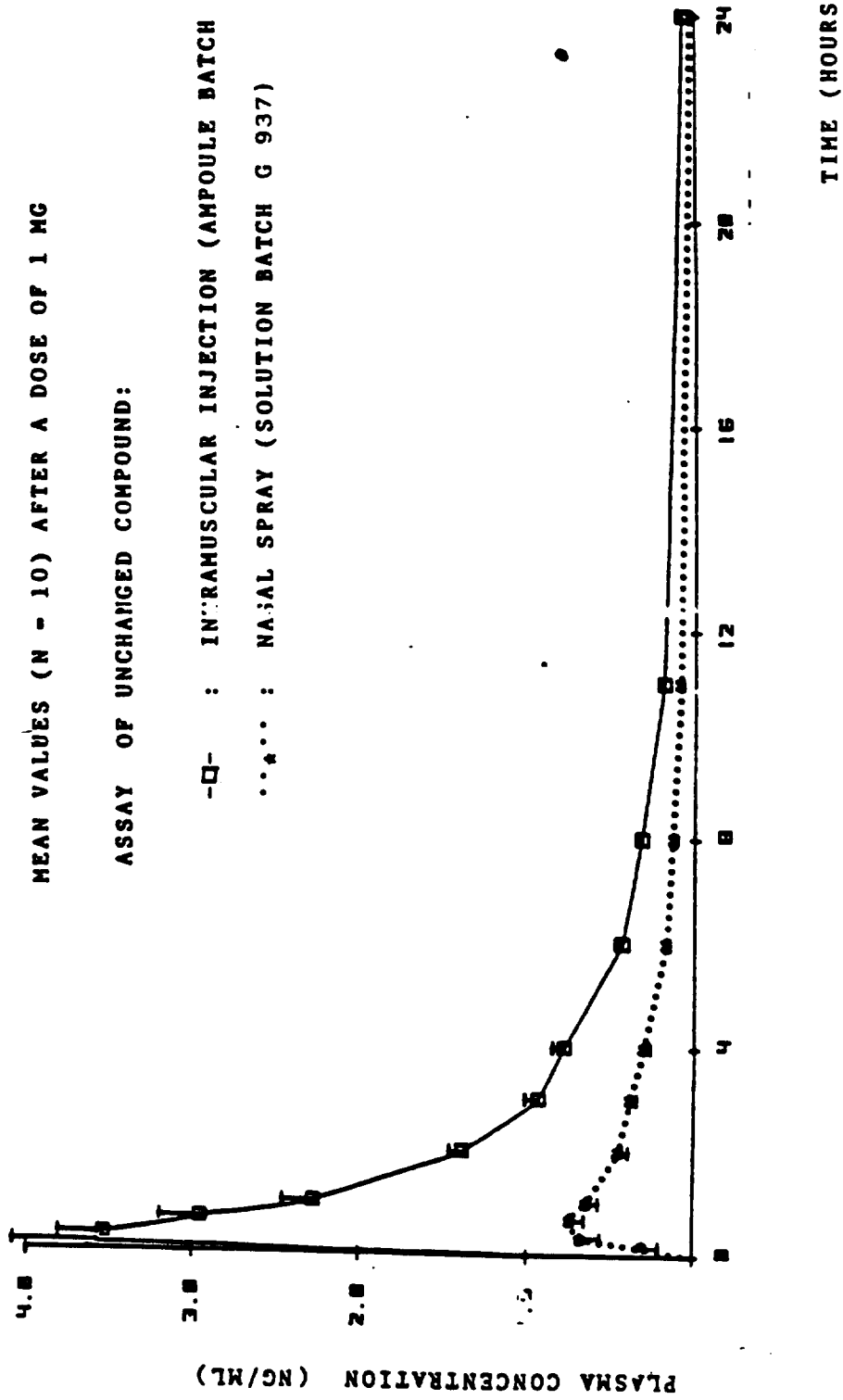
DIHYDROERGOTAMINE - COMPARISON OF BIOAVAILABILITY

MEAN VALUES (N = 10) AFTER A DOSE OF 1 MG

ASSAY OF UNCHANGED COMPOUND:

-□- : INTRAMUSCULAR INJECTION (AMPOULE BATCH 30)

..... : NASAL SPRAY (SOLUTION BATCH G 937)



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TABLE I

DIHYDROERGOTAMINE - COMPARISON OF BIOAVAILABILITY AFTER ADMINISTRATION BY TWO ROUTES
 PLASMA CONCENTRATION (NG/ML.) AFTER A DOSE OF 1 MG
 INTRAMUSCULAR INJECTION (AMPOULE BATCH 30)
 ASSAY OF UNCHANGED COMPOUND

Time(h)	M 536	F 365	M 283	F 461	F 506	M 512	M 557	M 558	F 562	F 531	Mean	SD	SEM
0.17											3.596	1.547	0.489
0.33											3.533	0.840	0.266
0.67											2.950	0.767	0.243
1.00											2.276	0.573	0.181
2.00											1.383	0.242	0.076
3.00											0.930	0.250	0.079
4.00											0.780	0.216	0.068
6.00											0.432	0.126	0.040
8.00											0.310	0.088	0.028
11.00											0.185	0.052	0.017
12.00											0.073	0.043	0.014
12.425	11.788	10.929	13.365	0.071	9.501	10.021	11.698	12.978	9.945	11.072	1.683	0.532	

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TABLE II

DIHYDROERGOTAMINE - COMPARISON OF BIOAVAILABILITY AFTER ADMINISTRATION BY TWO ROUTES
 PLASMA CONCENTRATION (NG/ML) AFTER A DOSE OF 1 MG
 NASAL SPRAY (SOLUTION BATCH G 937)
 ASSAY OF UNCHANGED COMPOUND

Time (H):	N 536	F 365	N 283	F 461	F 546	N 512	N 557	N 558	F 562	F 531	Mean	SD	SEM
0.17											0.395	0.316	0.100
0.33											0.676	0.390	0.123
0.67											0.740	0.286	0.091
1.00											0.638	0.230	0.073
2.00											0.449	0.189	0.060
3.00											0.384	0.140	0.047
4.00											0.301	0.125	0.040
6.00											0.170	0.076	0.024
8.00											0.127	0.066	0.021
11.00											0.089	0.065	0.020
14.00											0.021	0.027	0.008
U.C.	2.077	5.708	1.958	3.205	1.804	2.636	6.568	3.398	1.018	5.295	3.675	1.678	0.531

06-00602

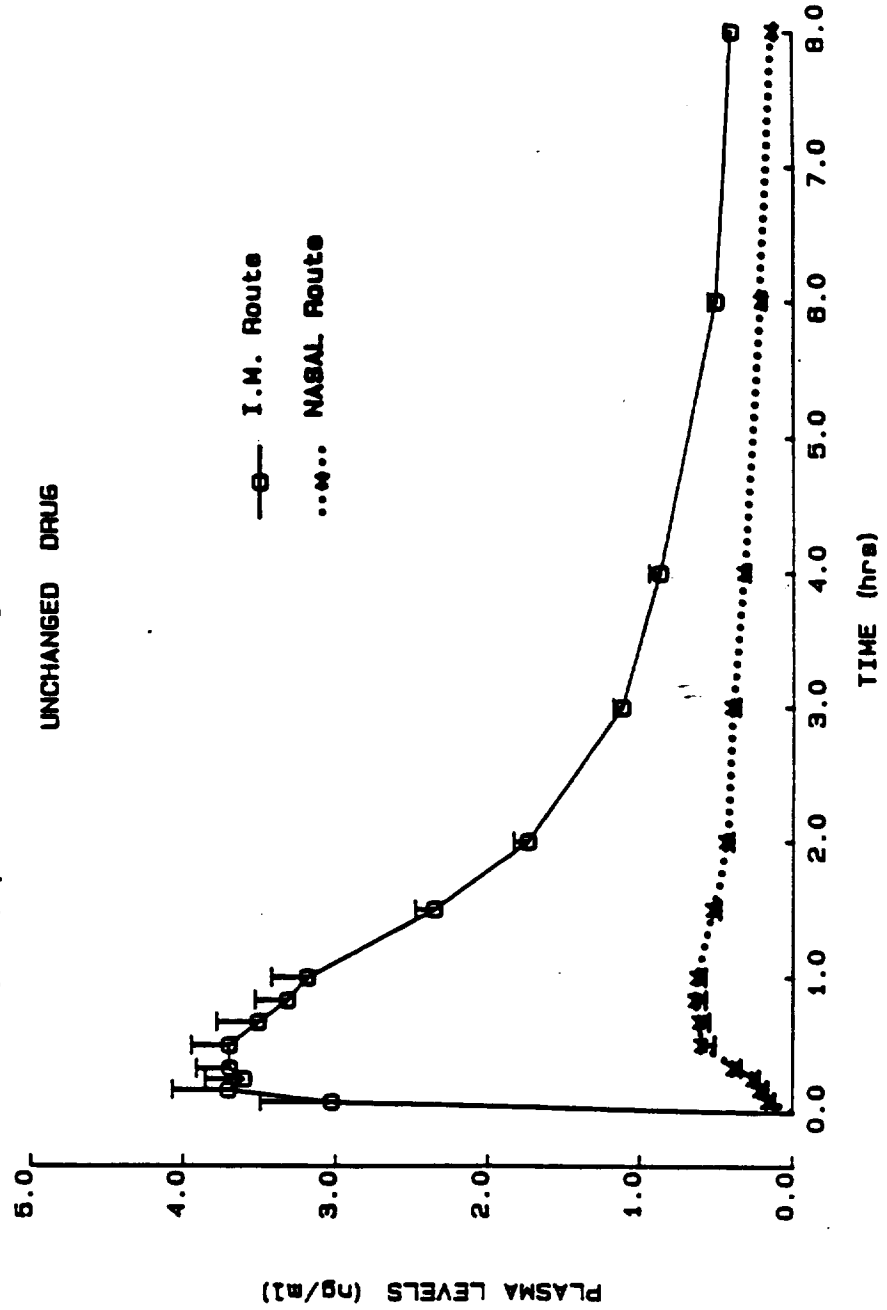
: Value below sensitivity of the method

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303-020
DIHYDROERGOTAMINE - STUDY 85.HOP.21.DHE

Mean + sem (n=18) plasma levels (ng/ml) after administration of 1 mg



SANDOZ C.R.P. RUELL MDC Study number : 85.HOP.21.DHE Table : I
 Compound : DIHYDROERGOTAMINE (n= 18) Dosage : 1 mg Single dose
 Form : INJECTION - Batch 51 1mg/ml Route : I.M.
 Mode : Method :

INDIVIDUAL PLASMA CONCENTRATIONS (ng/ml)

Sub. \ Tim	.08	.17	.25	.33	.50	.67	.83	1.00	1.50	2.00	2.60
01											
02											
03											
04											
05											
06											
07											
08											
09											
10											
11											
12											
13											
14											
15											
16											
17											
18											
Mean	3.029	3.706	3.604	3.697	3.700	3.511	3.319	3.190	2.352	1.734	1.116
SD	1.972	1.541	1.060	.911	1.041	1.139	.891	.977	.521	.406	.230
SEM	.465	.363	.250	.214	.245	.268	.210	.230	.123	.095	.052

SANDOZ C.R.P. RUEIL MDC Date : 4-21-1986 Study number : 85.HOP.21.DHE Table : I b1s
 Compound : DIHYDROERGOTAMINE Population : HEALTHY VOLUNTEERS (n= 18) Dosage : 1 mg Single dose
 Form : INJECTION - Batch 51 1mg/ml Method : I.M.

INDIVIDUAL PLASMA CONCENTRATIONS (ng/ml)

Sub. \ Tim	4.00	6.00	8.00	11.00	13.00	24.00	A.U.C.
01							
02							
03							
04							
05							
06							
07							
08							
09							
10							
11							
12							
13							
14							
15							
16							
17							
18							
Mean	.869	.504	.398	.279	.206	.081	13.566
SD	.297	.209	.136	.156	.135	.044	3.450
SEM	.070	.049	.032	.036	.031	.010	.813

SANDOZ C.R.P. RUE IL NDC Study number : 85.HOP.21.DHE Table : II
 Compound : DIHYDROERGOTAMINE (n= 18) Dosege : 1 mg Single dose
 Form : SPRAY - Batch 70479 4mg/ml Route : NASALE
 Date : 4-21-1986
 Population : HEALTHY VOLUNTEERS
 Method :

INDIVIDUAL PLASMA CONCENTRATIONS (ng/ml)

Sub. \ Tim	.08	.17	.25	.33	.50	.67	.83	1.00	1.50	2.00	3.00
01											
02											
03											
04											
05											
06											
07											
08											
09											
10											
11											
12											
13											
14											
15											
16											
17											
18											
Mean	.175	.225	.269	.399	.607	.623	.649	.635	.531	.446	.408
SD	.233	.245	.189	.229	.394	.308	.323	.254	.228	.218	.227
SEM	.055	.057	.044	.054	.092	.072	.076	.060	.053	.051	.053

- Value below the method sensitivity

SANDOZ C.R.P. RUELL
 Compound : DIHYDROERGOTAMINE
 Form : SPRAY - Batch 70479 4mg/ml
 MOC
 Date : 4-21-1986
 Population : HEALTHY VOLUNTEERS
 Method :
 Study number : 85.HOP.21.DHE
 (n= 18)
 Dosage : 1 mg Single dose
 Route : NASALE
 Table :II bis

INDIVIDUAL PLASMA CONCENTRATIONS (ng/ml)

Sub. \ Tim	4.00	6.00	8.00	11.00	13.00	24.00	A.U.C.
01							
02							
03							
04							
05							
06							
07							
08							
09							
10							
11							
12							
13							
14							
15							
16							
17							
18							
Mean	.326	.213	.136	.113	.101	.039	4.061
SD	.150	.126	.077	.069	.077	.027	1.724
SEM	.035	.029	.018	.016	.018	.006	.406

- Value below the method sensitivity

DIHYDROERGOTAMINE - STUDY 85-HQP-21-DHE

Individual and mean values of the really administered
dose of dihydroergotamine methane sulfonate

SUBJECT N°	Spray device before administration	weight (g) after administration	Δ weight (g)	Dose* (mg)
01				
02				
03				
04				
05				
06				
07				
08				
09				
10				
11				
12				
13				
14				
15				
16				
17				
18				
			Mean	0.8130
			SD	0.1233
			SEM	0.0291

*Solution 4 mg/ml of dihydroergotamine
methane sulfonate
Solution density : 1.023

Table XIII

DIHYDROERGOTAMINE - STUDY 85-HOP-21-DHE

RELATIVE BIOAVAILABILITY OF DHE

SUBJECTS	Without correction for the dose		corrected for the really administered dose	
	From PLASMA data*	From URINE data**	From PLASMA data*	From URINE data**
01				
02				
03				
04				
05				
06				
07				
08				
09				
10				
11				
12				
13				
14				
15				
16				
17				
18				
Arithmetic mean	31.3	32.1	38.4	40.7
SD	14.9	12.9	16.4	17.8
SEM	3.5	3.0	3.8	4.2
Geometric mean	28.1	29.5	34.9	36.6

* AUC (0-24 H) NASAL route versus I.M. route (%)

** Urinary excretion (0-72 H) NASAL route versus I.M. route (%)

STUDY # 303-022

303-022

Table : I

Study number :
 Dosage : 1 mg
 Route : NASAL

Date : 4-17-1986
 Population : HEALTHY VOLUNTEERS
 (n= 15)

Compound : DIHYDROERGOTAMINE
 Form : SPRAY - Batch 70479 4 mg/ml
 Mode : 0.5 mg , 0.5 mg 10 mn after

SANDOZ C.R.P. RUELL
 JJD
 Method :

INDIVIDUAL PLASMA CONCENTRATIONS (ng/ml) of DHE

Sub. \ Tim	.17	.33	.50	.67	.83	1.00	1.17	1.50	2.00	3.00	4.0
IF 302											
IF 673											
IH 664											
IF 656											
IH 702											
IH 651											
IF 648											
IF 709											
IH 705											
IH 714											
IF 697											
IF 698											
IH 706											
IF 712											
IH 713											
Mean	.051	.269	.434	.516	.567	.577	.525	.430	.313	.229	.21
SEM	.087	.228	.271	.270	.256	.245	.201	.176	.146	.089	.07
SEM	.022	.058	.070	.069	.066	.063	.051	.045	.037	.023	.01

- - Value below the method sensitivity

#303-022

Table : II

Study number : 85-CL1.10.DHE
 (n= 15)
 Doseage : 1 mg
 Route : NASAL

Date : 4-17-1986
 Population : HEALTHY VOLUNTEERS
 Method :

JJD
 SANDOZ C.R.P. RUEIL
 Compound : DIHYDROERGOTAMINE
 Form : SPRAY - Batch 70479 4 mg/ml
 Mode : 0.5 mg * 0.5 mg 10 mn after

INDIVIDUAL PLASMA CONCENTRATIONS (ng/ml) of DHE

ISub. \ Tim	6.00	8.00	11.00	13.00	24.00	A.U.C.
IF 302						
IM 673						
IM 664						
IF 656						
IM 702						
IM 651						
IF 648						
IF 709						
IM 705						
IM 714						
IF 697						
IF 698						
IM 706						
IF 712						
IM 713						
Mean	.147	.117	.078	.058	.028	2.812
SD	.057	.056	.041	.036	.020	1.197
SEM	.014	.014	.010	.009	.005	.309

SANDOZ C.R.P. RUEIL JJD
 Compound : DIHYDROERGOTAMINE
 Form : SPRAY - Batch 70479 4 mg/ml
 Mode : 1 mg + 1 mg 10 mn after

Date : 4-17-1986
 Population : HEALTHY VOLUNTEERS
 Method :

303-022
 Study number : 85.CLI.10.DHE
 Doseage : 2 mg Single dose
 Route : NASAL
 Table : III

INDIVIDUAL PLASMA CONCENTRATIONS (ng/ml) of DHE

Sub. \ Tim	.17	.33	.50	.67	.83	1.00	1.17	1.50	2.00	3.00	4.00
IF 302											
IF 673											
IM 664											
IF 656											
IM 702											
IM 651											
IF 648											
IF 709											
IM 705											
IM 714											
IF 697											
IF 698											
IM 706											
IF 712											
IM 713											
Mean	.129	.491	.885	.949	.949	.911	.912	.821	.600	.475	.465
SD	.143	.337	.523	.497	.497	.394	.366	.380	.321	.277	.319
SEM	.037	.087	.135	.128	.128	.101	.094	.098	.083	.071	.087

303-022
 85-CLJ.10.DHE
 2 mg Single dose
 NASAL

Date : 4-17-1986
 Population : HEALTHY VOLUNTEERS
 Study number : (n= 15)
 Doseage :
 Route :

JJD
 SANDOZ C.R.P. RUEIL
 Compound : DIHYDROERGOTAMINE
 Form : SPRAY - Batch 70479 4 mg/ml
 Mode : 1 mg + 1 mg 10 mn after

Table : IV

INDIVIDUAL PLASMA CONCENTRATIONS (ng/ml) of DHE

Sub. \ Tim	6.00	8.00	11.00	13.00	24.00	A.U.C.
IF 302						
IM 673						
IM 664						
IF 656						
IM 702						
IM 651						
IF 648						
IF 709						
IM 705						
IM 714						
IF 697						
IF 698						
IM 706						
IF 712						
IM 713						
Mean	.257	.204	.140	.103	.055	5.272
SD	.180	.161	.107	.060	.035	2.915
SEM	.046	.041	.027	.015	.009	.752

303-022
 85 CL 1.10 DHE
 4 mg Single dose
 NASAL

Table : V

SANDOZ C.P.P. RUEIL JJD
 Compound : DIHYDROERGOTAMINE
 Form : SPRAY - Batch 70479 4 mg/ml
 Mode : 2 mg • 2 mg Single dose
 Date : 4-12-1986
 Population : HEALTHY VOLUNTEERS
 Method :
 Study number : (n= 15)
 Dose :
 Route :

INDIVIDUAL PLASMA CONCENTRATIONS (ng/ml) of DHE

Sub. \ Tim	.17	.33	.50	.67	.83	1.00	1.17	1.50	2.00	3.00	4.00
IF 302											
IF 673											
IM 664											
IF 656											
IM 702											
IM 651											
IF 648											
IF 709											
IM 705											
IM 714											
IF 697											
IF 698											
IM 706											
IF 712											
IM 713											
Mean	.270	1.092	1.748	1.833	1.924	1.748	1.592	1.500	1.108	.832	.737
SD	.196	.677	.932	.932	.880	.782	.571	.575	.446	.271	.229
SEM	.050	.175	.240	.242	.227	.202	.147	.148	.115	.070	.059

303-022
 85-CL-10-DHE
 4 mg Single dose
 NASAL

SANDOZ C. R. P. RUEJL JJD
 Compound : DIHYDROERGOTAMINE
 Form : SPRAY - Batch 70479 4 mg/ml
 Mode : 2 mg + 2 mg Single dose

Date : 4-17-1986
 Population : HEALTHY VOLUNTEERS
 Method :

Study number :
 Dosage : (n= 15)
 Route :

Table :VI

INDIVIDUAL PLASMA CONCENTRATIONS (ng/ml) of DHE

Sub. \ Tim	6.00	8.00	11.00	13.00	24.00	A.U.C.
IF 302						
IF 673						
IM 664						
IF 656						
IM 702						
IM 651						
IF 648						
IF 709						
IM 705						
IM 714						
IF 697						
IF 698						
IM 706						
IF 712						
IM 713						
Mean	.444	.393	.236	.174	.088	9.312
SD	.181	.186	.083	.076	.043	3.285
SEM	.046	.048	.021	.019	.011	.848

SANDOZ C.R.P. RIJEIL JJD
 Compound : DIHYDROERGOTAMINE
 Form : SPRAY - Batch 70479 4 mg/ml
 Mode : 0.5 mg + 0.5 mg 10 mn after
 Date : 4-17-1986
 Population : HEALTHY VOLUNTEERS
 Method :
 Study number : (n= 15)
 Dosage : 1 mg Single dose
 Route : NASAL
 Table : VII
 303-022

BIOAVAILABILITY PARAMETERS

	C MAX	T MAX	A.U.C
IF 302			
IF 673			
IF 664			
IF 656			
IF 702			
IF 651			
IF 648			
IF 709			
IF 705			
IF 714			
IF 697			
IF 698			
IF 706			
IF 712			
IF 713			
Mean	1.022	2.812	
SD	.251	1.197	
SEM	.064	.309	

303-022
 85.CLI.10.DHE
 Table : X

Date : 2-21-1986
 Population : HEALTHY VOLUNTEERS (n= 15)
 Study number :
 Dosage :
 Route : NASAL

JJD

SANDOZ C.R.P. RUEIL
 Compound : DIHYDROERGOTAMINE
 Form : SPRAY Batch 70479
 Mode :

Method :

Administered doses determined by weighting (mg)

Sub. \ Tim | 1. | 2. | 4. |

IF 302
 IF 673
 IM 664
 IF 656
 IM 702
 IM 651
 IF 648
 IF 709
 IM 705
 IM 714
 IF 697
 IF 698
 IM 706
 IF 712
 IM 713

Mean | .9342 | 1.7545 | 3.6117 |
 SD | .1975 | .2237 | .2004 |
 SEM | .0510 | .0578 | .0517 |

303-022
 85.CLI.10.DHE
 4 mg Single dose
 NASAL

Study number :
 (n= 15)
 Doseage :
 Route :

Date : 4-17-1986
 Population : HEALTHY VOLUNTEERS
 Method :

SANDOZ C. R. P. RUEIL JJD
 Compound : DIHYDROERGOTAMINE
 Form : SPRAY - Batch 70479 4 mg/ml
 Mode : 2 mg + 2 mg Single dose

Table : IX

BIOAVAILABILITY PARAMETERS

	C	MAX	T	MAX	A.U.C
IF 302					
IM 664					
IF 656					
IM 702					
IM 651					
IF 648					
IF 709					
IM 705					
IM 714					
IF 697					
IF 698					
IM 706					
IF 712					
IM 713					
Mean	2.162		.778		9.312
SD	.885		.233		3.285
SEM	.228		.060		.848

303-022

85-CL1.10.DHE
2 mg Single dose
NASAL

Study number :
(n= 15)
Dosage :
Route :

Date : 4-17-1986
Population : HEALTHY VOLUNTEERS
Method :

JJD
Compound : DIHYDROERGOTAMINE
Form : SPRAY - Batch 70479 4 mg/ml
Dose : 1 mg x 1 mg 10 mn after

Table : VII

BIOAVAILABILITY PARAMETERS

	C	MAX	T	MAX	A.U.C	I
IF 302						
IF 673						
IM 664						
IF 656						
IM 702						
IM 651						
IF 648						
IF 709						
IM 705						
IM 714						
IF 697						
IF 698						
IM 706						
IF 712						
IM 713						
Mean	1.131			.878	5.272	
SD	.502			.285	2.915	
SEM	.129			.073	.752	