CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20420

CHEMISTRY REVIEW(S)

JUL 14 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-420 **CHEM.REVIEW #:** 6 **REVIEW DATE:** 9 Jul 97

SUBMISSION	TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		21 Dec 93		
AMENDMENT	NC	27 Jun 97	1 Jul 97	8 Jul 97

NAME & ADDRESS OF APPLICANT:

Gensia, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

DRUG PRODUCT NAME:

Proprietary:	GenESA System
Nonproprietary/USAN:	Arbutamine hydrochloride (USAN)
Code Name/#:	GP-2-121-3
Chem.Type/Ther.Class:	1 S

PATENT STATUS:

U.S. Patent 5,108,363 - "Diagnosis, Evaluation and Treatment of Coronary Artery Disease by Exercise Simulation Using Closed Loop Drug Delivery of an Exercise Simulating Agent Beta Agonist"
Expiration date: 28 Apr 09

PHARMACOL.CATEGORY/INDICATION: Diagnostic for coronary artery disease

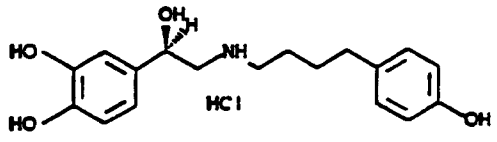
DOSAGE FORM: SVS

STRENGTHS: 0.05 mg/mL, 20 mL prefilled syringe

ROUTE OF ADMINISTRATION: Intravenous infusion

DISPENSED: _x_ Rx ___ OTC

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



R-1-(3,4-Dihydroxyphenyl)-2-[4-(4-hydroxyphenyl)butylamino]ethanol Hydrochloride

$C_{18}H_{23}NO_4 \cdot HCl$ 353.85 (base, 317.37)

NDA 20-420 Gensia GenESA

CONCLUSIONS & RECOMMENDATIONS:

APPROVABLE in regard to the CMC section of the application.

The applicant should be notified that we recommend they use the phrase "arbutamine hydrochloride injection" in their labels and labeling.

Orig. NDA
HFD-110/Division File
HFD-110/JShort/7/8/97
~~HFD-110/CSO~~
HFD-810/CHoiberg

R/D Init by: RWolters/7/10/97

James H. Short, Ph.D., Review Chemist
filename: **N20-420.CR6**

for applicant 7/14/97

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JUN 27 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-420 **CHEM.REVIEW #:** 5 **REVIEW DATE:** 25 Jun 97

SUBMISSION	TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		21 Dec 93		
AMENDMENT	AL	19 Jun 97	20 Jun 97	25 Jun 97

NAME & ADDRESS OF APPLICANT:

Gensia, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

DRUG PRODUCT NAME:

Proprietary:	GenESA System
Nonproprietary/USAN:	Arbutamine hydrochloride (USAN)
Code Name/#:	GP-2-121-3
Chem.Type/Ther.Class:	1 S

PATENT STATUS:

U.S. Patent 5,108,363 - "Diagnosis, Evaluation and Treatment of Coronary Artery Disease by Exercise Simulation Using Closed Loop Drug Delivery of an Exercise Simulating Agent Beta Agonist"
Expiration date: 28 Apr 09

PHARMACOL.CATEGORY/INDICATION: Diagnostic for coronary artery disease

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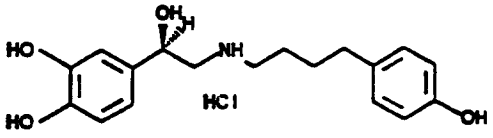

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$C_{18}H_{23}NO_4 \cdot HCl$ 353.85 (base, 317.37)

NDA 20-420 Gensia GenESA

CONCLUSIONS & RECOMMENDATIONS:

APPROVABLE in regard to the CMC section of the application.

Orig. NDA
HFD-110/Division File
HFD-110/JShort/4/5/96
HFD-110/CSO
HFD-810/CHoiberg

R/D Init by: RWolters/

James H. Short, Ph.D., Review Chemist
filename: **N20-420.CR4**

4/5/96

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

OCT 24 1994

NDA #: 20-420 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 17 Oct 94

SUBMISSION	TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		21 Dec 93		
AMENDMENT	BC	19 Sep 94	20 Sep 94	23 Sep 94

NAME & ADDRESS OF APPLICANT:

Gensia, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

DRUG PRODUCT NAME:

Proprietary:	GenESA System
Nonproprietary/USAN:	Arbutamine hydrochloride (USAN)
Code Name/#:	GP-2-121-3
Chem.Type/Ther.Class:	1 S

PATENT STATUS:

U.S. Patent 5,108,363 - "Diagnosis, Evaluation and Treatment of Coronary Artery Disease by Exercise Simulation Using Closed Loop Drug Delivery of an Exercise Simulating Agent Beta Agonist"
Expiration date: 28 Apr 09

PHARMACOL.CATEGORY/INDICATION: Diagnostic for coronary artery disease

DOSAGE FORM: SVS

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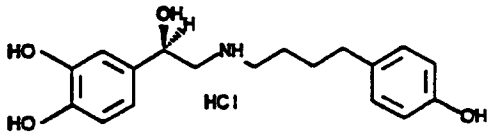

R-1-(3,4-Dihydroxyphenyl)-2-(4-(4-hydroxyphenyl)butylamino)ethanol Hydrochloride

$C_{18}H_{23}NO_4 \cdot HCl$ 353.85 (base, 317.37)

both the drug substance and the drug product. Part III contains revisions in the container/closure system.

CONCLUSIONS & RECOMMENDATIONS:

NOT APPROVABLE

The application will be approvable as far as the CMC section is concerned when a satisfactory inspection is completed, and satisfactory reviews of the EA and microbiological sections have been received. Validation of the analytical control procedures will be requested.

The following should be added to the storage statement on the labels and Package Insert, "Protect from Light," in view of the fact that photolability is observed even when the syringes are stored in their cardboard containers.

Orig. NDA
HFD-110/Division File
HFD-110/JShort/9/28/94
HFD-110/CSO
District

R/D Init by: RWolters/10/20/94

James H. Short, Ph.D., Review Chemist
filename: **N20-420.CR3**

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

JUL 20 1994

NDA #: 20-420 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 7 Jul 94
REVISED: 18 Jul 94

SUBMISSION	TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		21 Dec 93		
AMENDMENT	BC	10 May 94	13 May 94	16 May 94

NAME & ADDRESS OF APPLICANT: Gensia, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

DRUG PRODUCT NAME:

Proprietary:	GenESA System
Nonproprietary/USAN:	Arbutamine hydrochloride (USAN)
Code Name/#:	GP-2-121-3
Chem.Type/Ther.Class:	1 S

PATENT STATUS: U.S. Patent 5,108,363 - "Diagnosis, Evaluation and Treatment of Coronary Artery Disease by Exercise Simulation Using Closed Loop Drug Delivery of an Exercise Simulating Agent Beta Agonist"
Expiration date: 28 Apr 09

PHARMACOL.CATEGORY/INDICATION: Diagnostic for coronary artery disease

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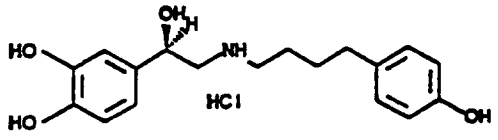

R-1-(3,4-Dihydroxyphenyl)-2-(4-(4-hydroxyphenyl)butylamino)ethanol Hydrochloride

$C_{18}H_{23}NO_4 \cdot HCl$ 353.85 (base, 317.37)

NDA 20-420 Gensia GenESA

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/6/14/94
HFD-110/CSO
District

R/D Init by: RWolters7/13/94

James H. Short

James H. Short, Ph.D., Review Chemist
filename: N20-420.CR2

Review of Chemistry, Manufacturing, and Controls

MAR - 1 1994

NDA #: 20-420 **CHEM.REVIEW #:1** **REVIEW DATE:** 18 Feb 94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	21 Dec 93	21 Dec 93	23 Dec 93

NAME & ADDRESS OF APPLICANT: Gensia, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

DRUG PRODUCT NAME:

Proprietary: GenESA System
Nonproprietary/USAN: Arbutamine hydrochloride (USAN)
Code Name/#: GP-2-121-3
Chem.Type/Ther.Class: 1 S

PATENT STATUS: U.S. Patent 5,108,363 - "Diagnosis, Evaluation and Treatment of Coronary Artery Disease by Exercise Simulation Using Closed Loop Drug Delivery of an Exercise Simulating Agent Beta Agonist"
Expiration date: 28 Apr 09

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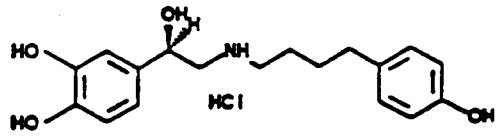

R-1-(3,4-Dihydroxyphenyl)-2-(4-(4-hydroxyphenyl)butylamino)ethanol Hydrochloride

$C_{18}H_{23}NO_4 \cdot HCl$ 353.85 (base, 317.37)

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: Microbiology
Environmental Assessment

REMARKS/COMMENTS:

The application provides for the GenESA System, which combines the catecholamine, arbutamine hydrochloride, with a closed-loop, computer-controlled drug delivery device. The prefilled syringe is intended for intravenous infusion only with the GenESA Device.

The application is being reviewed concurrently by CDRH.

The applicant includes a statement that a copy of the CMC section was sent to the District Office (v. 1.4, p. 4). I confirmed by telephone 12 Jan 94 that LOS-DO had received a copy.

A "Request for Trademark Review" will be sent to the Labelling and Nomenclature Committee.

The applicant will be asked to confirm that the copy provided to the district is identical to the archival copy.

CONCLUSIONS & RECOMMENDATIONS:

The deficiencies noted in the review of this application will be conveyed to the applicant.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/1/5/94
HFD-110/CSO
District
HFD-102/CKumkumian
R/D Init by: RWolters/2/25/94

James H. Short, Ph.D., Review Chemist
filename: **N20-420.CR1**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20420

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-420

GenESA SYSTEM™

(arbutamine HCL)

Infusion 0.05 mg/mL

HFD-110

Division of Cardio-Renal Drug Products

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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FINDING OF NO SIGNIFICANT IMPACT

for

NDA 20-420

GenESA SYSTEM™

(arbutamine HCL)

Infusion 0.05 mg/mL

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for GenESA SYSTEM™ , Gensia, Inc. has conducted a number of environmental studies and prepared an environmental assessment in accordance with *21 CFR 25.31a(a)* (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Arbutamine, a beta-adrenergic agonist, is a chemically synthesized drug which is administered as a 0.05 mg/mL injectable aqueous solution. The diagnostic procedure in which arbutamine is used is an adjunct to echo cardiography and radionuclide myocardial perfusion imaging The drug substance is manufactured b The finished product will be formulated and packaged at Gensia Laboratories, Ltd. The finished drug product will be used in hospitals, clinical cardiology units, and in the private offices of cardiologists throughout the United States.

Drug substance is extensively metabolized in humans, and only 10 percent of a ^{14}C labelled dose is recovered as intact arbutamine in the urine. Chemical and physical test results indicate that arbutamine will most likely be restricted to the aquatic environment and will be rapidly depleted by photodegradation and other environmental processes such as biodegradation because of arbutamine's structural similarity to naturally occurring catecholamine of established biodegrability. This environmental assessment would qualify under Tier 0 in the Guidance for Industry (61 FR 1031, 1996) and no fate and effects testing would be necessary.

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Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of through a glass crusher by flushing with copious amounts of water that are then sewered to the waste treatment facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From private offices of a cardiologist use, the packaging containers, exclusive of medical waste, will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, ~~while minimal quantities of unused drug may be disposed of in the sewer system.~~

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

1/26/96
DATE

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

1/29/96
DATE

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

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

HFD-110 /CSO copy to NDA 20-420
HFD-357/FONSI File
HFD-357/Docket File
HFD-019/FOI COPY

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GenESA SYSTEM
(Arbutamine)

Amendment to NDA 20-420
Response to December 15, 1994 Letter

Volume 13
Table of Contents

Environmental Assessment for Arbutamine

Volume 13
Table of Contents (Cont'd)

ENVIRONMENTAL ASSESSMENT FOR ARBUTAMINE

1. DATE

April 20, 1995

2. NAME OF APPLICANT

Gensia, Inc.

3. ADDRESS

9360 Towne Centre Drive
San Diego, CA 92121

4. DESCRIPTION OF THE PROPOSED ACTION

4.1 REQUIRED APPROVAL

Approval is sought to manufacture and distribute arbutamine in an injectable aqueous solution. Arbutamine (as its hydrochloride) was formulated with several excipients into an aqueous solution that is filled into 20-ml syringes. The concentration of arbutamine in the syringes is 0.05 mg/mL (expressed as the hydrochloride). The estimated requirement based on the projected sales volume of the new drug is given in Appendix C (confidential). This document consists of a full Environmental Assessment.

4.2 NEED FOR ACTION

Arbutamine is a beta-adrenergic agonist. Its administration to human subjects brings about a physiological state of simulated physical activity. The diagnostic procedure in which it is used is an adjunct to echo cardiography and radionuclide myocardial perfusion imaging. The use of arbutamine is especially indicated for the evaluation of patients (with known or suspected coronary artery disease) who cannot perform strenuous physical activity.

4.3 LOCATIONS OF MANUFACTURE

Synthesis of the drug substance for this product will be carried out at [redacted]. The finished product will be formulated and packaged at Gensia Laboratories, Ltd., 19 Hughes Drive, Irvine, California 92718.

4.4 LOCATIONS OF PRODUCT USE AND DISPOSAL

The pre-filled syringes of arbutamine in water will be used in hospitals, clinical cardiology units, and in the private offices of cardiologist. There are 16,000 cardiologists in the United States and approximately 6 million patients who could use their diagnostic services. The used syringes that had contained the solutions of arbutamine will be disposed of a medical waste from the individual sites of their use.

Production rejects (at Gensia Laboratories) and returned goods will be disposed of through a glass crusher by flushing with copious amounts of water that are then sewered to the waste treatment facility of the Irvine Ranch Water District. The account number for both potable water and sewage treatment is 38-040930-01-8. The account is renewed annually. Additional information on disposal of waste water is discussed in Subsection 6.2.

4.5 ENVIRONMENTAL SETTING OF FACILITIES

4.5.1

4.5.2 Gensia Laboratories

Gensia Laboratories Ltd. is located in the County of Orange, California in the City of Irvine. The manufacturing complex is located at 19 Hughes in the Irvine Spectrum, a commercial development consisting primarily of light industry.

The City of Irvine is located in the Trabuco Plain approximately 5-10 miles from the Southern California coast at an elevation of approximately 500 feet. Elevations within the city limits range from 100-3000 feet above sea level.

The Orange County area of Southern California is characterized by a moderate climate with a mean annual temperature of 62 - 67^0 F. The annual rainfall is approximately 14.5 inches; wind direction is predominately west to northwest at a mean hourly speed of approximately 6 miles per hour.

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

The drug that is the subject of the proposed action is arbutamine.

The molecular structures of arbutamine and some related chemicals are shown in Figure 5-1.

5.1 NOMENCLATURE

5.1.1 Chemical Abstracts (Tenth Collective Index)

(R)-4-[1-hydroxy-2-[[4-(4-hydroxyphenyl)-butyl]amino]ethyl]-1,2-benzenediol hydrochloride

5.1.2 United States adopted Name (USAN)

Arbutamine

5.1.3 CAS Registry Number

125251-66-3

5.1.4 Code Name

GP-2-121-3

5.1.5 Molecular Formula and Weight

$C_{18}H_{24}NO_4Cl$ MW = 353.85 (hydrochloride)

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Secret

Information

5.2 PHYSICAL DESCRIPTION

Arbutamine is a white to off-white solid with a relatively high melting point. Its chemical and physical properties are listed in Table 5-1. In aqueous solution, it dissociates into its salt and amine free base form. The relative concentration of the drug substance that will be present as the salt and free base form at the pH of an aquatic system can be calculated as follows:

$$\frac{[Salt]}{[Base]} = \frac{[K_a]}{[H^+]}$$

where:

[Base] = molar concentration of drug substance present as free base.

[Salt] = molar concentration of drug substance present as an amine salt.

$[H^+]$ = molar concentration of hydrogen ions (i.e., the reciprocal of the antilog pH).

K_a = equilibrium constant for acidic dissociation of the acid (i.e., the reciprocal of the antilog pK_a).

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CHEMICAL AND PHYSICAL PROPERTIES OF ARBUTAMINE

TABLE 5-1

Molecular Formula	$C_{18}H_{24}NO_4Cl$
Molecular Weight	353.85
Melting Range	135 - 150°C
Solubility in Water	>300g/L (23°C)
Density	Not Determined
Vapor Pressure	Not Determined
Octanol-Water Partition Coefficient	0.52 (pH 7)
Acidic Dissociation (pK_a)	8.5
Electromagnetic Absorption (>290 nm)	Shoulder

From this relationship, the ratio of salt to amine free base at pH 5 is 3160; at pH 7, 32; and at pH 9, 0.32.

The vapor pressure of arbutamine is not determined, because it cannot be related to the volatility of the drug substance in the aquatic environment. Estimations of volatility from surface water that are based on vapor pressure (and a calculated Henry's constant) assume that the dissolved chemical is not ionic and does not become adsorbed to suspended particulates or sediment (Mackay and Wolkoff, 1973; Lyman et al., 1982). If the chemical is predominately ionic and also becomes adsorbed to the sediment of surface waters that receive sewage effluent--as would arbutamine (Item 7, Subsection C.7.2.5)--its volatilization to the atmosphere cannot be regarded as an operative process and, therefore, can no longer be estimated. These restrictive conditions are often overlooked in the widespread application of this model.

5.3 Additives

In addition to arbutamine, preparation of the injectable product requires water, sodium metabisulfite, citric acid monohydrate, disodium edetate, sodium chloride, and sodium citrate dihydrate. The CAS Registry Numbers are as follows:

- Sodium metabisulfite 7681-57-4
- Citric Acid 77-92-9
- Disodium edetate 139-33-3
- Sodium chloride 7647-14-5
- Sodium citrate 68-04-2

5.4 Impurities

No impurities have been identified in the product other than arbutamine sulfonate (Figure 5-1), which is formed in trace amounts by the reaction of arbutamine with the bisulfite ion present in the aqueous formulation. No CAS Registry Number is available for this impurity.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 SUBSTANCES EMITTED DURING MANUFACTURING

6.1.1 Preparation of the Drug Substance

The chemical reactions for synthesis of arbutamine, chemical substances associated with the manufacture of the bulk drug and material balance are listed in Appendix C (confidential).

6.1.2 Preparation of Arbutamine Injection

The material balance for the preparation of the drug product is provided in Appendix C (confidential).

Production rejects (at Gensia Laboratories) and returned goods will be disposed of through a glass crusher by flushing with copious amounts of water that are then sewered to the waste treatment facility of the Irvine Ranch Water District. The account number for both potable water and sewage treatment is 38-040930-01-8. The account is renewed annually.

6.2 CONTROLS EXERCISED ON RESIDUALS AND EMISSIONS

Safety precautions for handling the chemicals listed in the material balances are described in the Material Safety Data Sheets for these compounds. The MSDS for arbutamine is provided in Appendix F. Air emissions will be controlled as required by the Operating Permit from the Illinois Environmental Protection Agency and South Coast Air Quality Management District (Table 6-1). Records of emissions are maintained and inspected. Wastestreams will be sewered. These wastestreams will be chemically and biologically treated in Abbott's onsite facility before being released to the North Shore Sanitary District (Russell Road, Curnee, Illinois 60031). Gensia's waste water will be directly discarded to Irvine Ranch Water District. Solid waste is landfilled by Waste Management of Wisconsin and Irvine Bee Canyon Class II landfill.

6.3 COMPLIANCE OF PROPOSED ACTION WITH APPLICABLE EMISSION REQUIREMENTS

Equipment in which the drug substance and product will be manufactured is all properly permitted for air emissions (Table 6-1). Permit modifications can be requested (as needed) to correspond to changes in facility usage. The permit number for release of effluent from Abbott's wastewater treatment plant to the North Shore Sanitary District is 93-5A.

TABLE 6-1
Permits for Air, Liquid and Solid Emissions

Abbott

	Permit Number	Issuing Agency	Expiration Date
Air	097125AAA	Illinois EPA	June 10, 1998
Wastewater	93-5A	North Shore Sanitary District.	June 30, 1995
Solids	3062	Department of Natural Resources, State of Wisconsin	Renewed annually by Waste Management of Wisconsin on 9/30

Gensia

Air Quality

- South Coast Air Quality Management District

Air Quality Permits

Permit No.	Description	Expiration Date
D52887		8/1/95
D52888		8/1/95
D52889		8/1/95
D52890		8/1/95
D42877		8/1/95
D42868		8/1/95
D63207		8/1/95
D63208		8/1/95
D66081		8/1/95

TABLE 6-1 (Cont'd)
Permits for Air, Liquid and Solid Emissions

Water Quality

- Irvine Ranch Water District

Industrial Sewer Discharge Permit

Hazardous Materials

- Orange County Fire Department

Storage and Use of Hazardous Materials-Permits renewed annually.

Type Permit	Permit No.	
Haz Mat Storage	801031	7/21/95
High Pile Storage	81103	9/15/95
Corrosives	80103A	9/15/95
Other Health Haz	80103H	9/15/95
Cryogens, Non-Flammable	75103A	2/15/96
Compressed Gas	74103C	3/17/95
Flammable/Combustible	79103C	3/17/95
Welding & Cutting	49101	3/17/95
Flammable Liquid	79103D	7/21/95
Water Reaction	80103E	7/21/95
Toxics	80103J	7/21/95
Highly Toxics	80103F	9/16/95

The account number for release of wastewater to the waste treatment facility at the Irvine Ranch Water District by Gensia is 38-040930-01-8. Wastewater from manufacturing must meet the General Pretreatment Standards in 40 CFR Part 403 and the Effluent Guidelines and Standards for Pharmaceutical Manufacturing in 40 CFR Part 439. Landfilling of solid waste by Waste Management of Wisconsin is permitted by the State of Wisconsin, Department of Natural Resources and the state of California, Department of Toxic Substance Control. (Table 6-1).

Certification of compliance with applicable emission requirements is provided in Appendix E.

6.4 EFFECT OF PROPOSED ACTION ON COMPLIANCE WITH CURRENT EMISSION REQUIREMENTS

If modification of the current air permit is required, it will be processed with sufficient time to allow production to proceed. Modifications can be prepared by within 30 days and would be reviewed by the Illinois Environmental Protection Agency within 90 days. The facility permit for release of treated effluent to the will not be exceeded by the proposed manufacturing. Similarly, the generation of solid waste will not affect the permit for landfilling. For Gensia, the proposed action will not require any permit changes.

6.5 OCCUPATIONAL SAFETY

Employee education on health and safety is provided through lectures and hands-on training. Work procedures (including the use of uniforms, respirators, gloves, safety shoes, and eye protection) and engineering controls designed for the equipment (e.g., exhausts to remove dust) are adequate to ensure employee safety.

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ON ORIGINAL

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 facilities, and Material Safety Data Sheets are available to personnel for chemicals handled in the manufacturing area. Industrial hygienists routinely monitor the exposure of employees to any hazardous materials. Personnel also participate in annual physical evaluations. At Abbott and Gensia Laboratories, the Occupational Safety and Health Act is the principal set of regulations that are followed for protection of workers. No permits for worker safety are required. The facilities are also subject to the Illinois Chemical Safety Act and the Illinois Toxic Substances Disclosure to Employees Act. The Gensia facilities are subject to California Chemical Safety Act and The California Toxic Substances Disclosure to Employees Act.

The safe transport of all drug-related materials is ensured by following protocols which include formal qualification of vendors, training of personnel, and rigid specification of containers and materials. Access to drug substances and products is restricted to authorized personnel.

6.6 AMOUNT OF SUBSTANCES ENTERING THE ENVIRONMENT

Arbutamine is extensively metabolized in humans, and only 10 percent of a ^{14}C labelled dose is recovered as intact arbutamine in the urine. The major metabolites of arbutamine identified in the urine were water soluble glucuronide conjugates of methoxyarbutamine and 2-keto arbutamine which accounted for 64% and 30%, respectively, of the total urinary ^{14}C activity.

The two routes by which arbutamine and its metabolites can enter the environment are: (1) elimination from patients who have received injections of the product and (2) release of wastewater from manufacturing. Introduction to sewage systems via human patients will account for most of these releases. Concentrations estimated in the following subsections are calculated as if degradation of arbutamine and its metabolites were not occurring, i.e., the concentrations are worst-case estimates. The effect of environmental processes on the dissipation of the released substances is discussed in Item 7 (Subsection 7.2).

6.6.1 Human Elimination

The estimate the amount of arbutamine and its metabolites (combined) entering a typical wastewater treatment plant based on product sales forecasts are provided in Appendix C (confidential).

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

In Item 7, information is presented that is relevant to the environmental transport and fate of arbutamine (and the volatile organic materials produced or utilized during manufacturing). Assessment of their transport and fate is accomplished through an evaluation of processes affecting transport (between air, water, and soil) and processes affecting structural degradation. These processes include photolysis, oxidation, hydrolysis, volatilization, sorption, bioaccumulation, and biodegradation. The evaluation of these processes is usually systematized by placing them in a format requiring discrete analysis of a chemical's potential for change within each process. In this way, the principal processes that constitute the pathways by which the chemical is environmentally dissipated can be identified. The methodology involved in this evaluation and its application to specific chemicals is discussed in Water-Related Environmental Fate of 129 Priority Pollutants (USEPA, 1979).

7.1 AIR

Little or no atmospheric emission of arbutamine occurs during synthesis of the drug substance, preparation of the product, or use of the product by patients. Arbutamine is an amine salt under most ambient environmental conditions. As such, it cannot volatilize from water or soil (Subsection 7.2.4). Dust from the manufacturing facilities is trapped by vent filters that are collected for landfilling. If any drug-containing dust should escape the filtration system, it would undergo oxidation in the atmosphere or be precipitated with rain. Then, after becoming adsorbed to soil, it would undergo biodegradation (Subsection 7.2.7).

The principal fate of the volatile organic materials (Subsection 6.1.1) is reaction with the oxidizing radical species of the atmosphere. The environmental fate of these solvents is described in the Hazardous Substances Databank (1992) and Howard et al (1990). The atmospheric half-lives (in days) from these data bases are: acetone (22), ethanol (6), and methanol (17.8).

7.2 WATER

Arbutamine and its metabolites can be released to publicly owned wastewater treatment plants via elimination by patients throughout the United States. Adsorption of arbutamine to the sewage sludge and biodegradation of it and its metabolites are expected to decrease their concentrations before the sewage effluent is released to surface water (Subsections 7.2.5 and 7.2.7). However, if processes leading to abatement are not considered, a worst-case concentration for a typical surface water can be estimated.

From Item 6 (Subsection 6.6.1), the worst-case concentration of arbutamine and its metabolites (combined) at a typical wastewater treatment plant that could result from the proposed action would range from 0.06 ng/L to 0.13 ng/L. Because of variations in plant capacity and in rates of surface water flow, dilution factors for effluent 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). The dilution factor for many rivers of the United States is 10^{-3} and, thus, the typical worst-case, combined concentration of arbutamine and its metabolites in surface waters that receive sewage land effluent could range from 0.06 pg/L to 0.13 pg/L. It should be noted, moreover, that the concentration would decrease downstream from the effluent outfall.

Arbutamine is not expected to survive passage through the wastewater treatment plants of and the
Nonetheless, a worst-case effect of unabated manufacturing releases from on the concentration of arbutamine in the Des Plaines River--the surface water that receives effluent from the can be estimated with a similar calculation. From Subsection C.6.6.2, the worst-case concentration of arbutamine (at that could be due to year 2000 releases (if onsite treatment had no effect) would be 0.025 ug/L. The effluent from this wastewater facility is discharged to the Des Plaines River which (near) has a flow rate of 189 ft^3/sec or 122 million gal/day. Therefore, the dilution factor from the facility (19 million gal/day) to the river is 1.6×10^{-1}, and the worst-case concentration of arbutamine at the outfall in the river (due to approval of the proposed action) would be 0.004 ug/L.

In the water of a sewage treatment facility, or in the surface water that dilutes the effluent, arbutamine and its metabolites could be affected by environmental processes that include photolysis, oxidation, hydrolysis, volatilization, adsorption, bioaccumulation, and biodegradation. These processes are evaluated individually (in the following subsections) before a concluding statement is made on the probable fate and concentration of released substances in the aquatic environment.

7.2.1 Photolysis

The electromagnetic absorption spectrum of arbutamine exhibits absorption within the wavelength range of terrestrial sunlight (Table 5-1). Therefore, its photodegradation in surface water is expected. The metabolites also have the same UV-chromophore, affect show absorption at wavelengths above 290 nm. The pivotal study for predicting arbutamine's lack of persistence in the aquatic environment is photolysis. A photolysis study (Environmental Assessment Technical Assistance Document, 3.10 (1995) Photodegradation) has demonstrated the photoability of arbutamine. (See Appendix B)

Below is an summary of the experimental results for the photolysis study with arbutamine. The study was conducted in three sections: an exposure of arbutamine in pH 5 buffer with an actinometer solution of PNAP, an exposure of arbutamine in pH 7 buffer with an actinometer solution of PNAP, and an exposure of arbutamine in pH 9 buffer with an actinometer solution of PNA. The photolytic rate constants for the light-exposed replicates at pH 5, 7 and 9 below have been corrected for the degradation observed in the dark control replicates.

Type of Solution		Coefficient of Determination (r^2)	Rate Constant (day $^{-1}$)	Half-Life $T_{1/2}$ (day)
pH 5	light	0.986	0.133	5.22
PNAP	light	0.987	0.0752	9.22
pH 7	light	0.983	0.578	1.20
PNAP	light	0.962	0.224	3.10
pH 9	light	0.958	5.14	0.135
PNA	light	0.985	5.27	0.132

The data show that arbutamine is rapidly degraded by the action of sunlight with a half-life of 1.2 day at pH 7. Therefore, arbutamine is expected to be photolyzed rapidly in natural bodies of water.

7.2.2 Oxidation

Photochemically produced hydroxyl radicals in water have been observed to oxidize many organic chemicals, including catecholamines (Dorfman and Adams, 1973; Wollman, Grunert and Rudolf, 1978; Trautner and Bradley, 1951). This reaction is thought to proceed via abstraction of hydrogen from the phenolic hydroxyl group. Hydroxyl radicals (and alkylperoxy radicals) are generated in surface water from the photolysis of naturally occurring substances that absorb terrestrial sunlight (Mill et al., 1980). These oxidants may be significant for the degradation of arbutamine and its metabolites in surface waters with an insufficient microbial population to promote biodegradation. Arbutamine degrades with a half-life of approximately 3 day at pH 7 in the absence of light. (Appendix B).

7.2.3 Hydrolysis

Based on the molecular structures of arbutamine, there are no functional groups present that can be displaced by water or hydroxide ion under ambient environmental conditions. Therefore, hydrolysis cannot occur.

7.2.4 Volatilization

Transport from water (or soil) to the atmosphere is not a relevant process for the environmental disposition of arbutamine or its metabolites. The pK_a value (8.5) from Table 5-1 indicates that arbutamine would be present in surface water primarily as a nonvolatile amine salt. Similarly, the metabolites of arbutamine would also be present in aquatic systems as ionic species, precluding their volatilization as well.

7.2.5 Sorption/Desorption

The log soil adsorption coefficient, log K_{oc} of arbutamine can be calculated from the following equation (Lyman et al., 1982):

$$\log K_{oc} = 0.524 \log K_{ow} + 0.855$$

$$(r^2 = 0.84; n = 30)$$

where:

K_{ow} = the octanol-water partition coefficient.

r^2 = the coefficient of determination (proportionate reduction in error).

n = the number of chemicals from which the regression was developed.

Using the log octanol-water partition coefficient (log 0.52) from Table 5-1, the log K_{oc} calculated by this method is 0.71. From this value, the distribution coefficient, K_d, for partitioning between surface water and sediment can be estimated by assuming a 4 percent organic content in the sediment. This is the assumption used in the ENPART model recommended in USFDA (1987). The relationship between K_{oc} and K_d is given by the following equation (Lyman et al., 1982):

$$Kd = Koc(OC)$$

where:

OC = the fractional amount of organic carbon in sediment.

The distribution coefficient, K_d, estimated by this method is 0.2 indicating that arbutamine could become adsorbed to sewage sludge or the sediment of quiescent surface waters. Biodegradation would be the expected fate of adsorbed arbutamine.

7.2.6 Bioaccumulation/Bioconcentration

Surface water bioconcentration of arbutamine is not expected due to the rapid photo degradation discussed under section 7.2.1

7.2.7 Biodegradation

The molecular structure of arbutamine is very similar to the structures of several naturally occurring catecholamines (Figure 5-1). This structural similarity to several natural products means that pathways for the environmental biodegradation of arbutamine are available, and the impact of its releases is thus diminished. As instructed in the Environmental Technical Assistance Handbook (USFDA, 1987), information on structurally similar chemicals can be used to predict the environmental fate of arbutamine and its metabolites.

Catechol amines are widespread in nature. Of the detected acids that are structurally similar to arbutamine, five are listed in Figure 5-1. One of them, epinephrine, differs only by the length of the carbon chain attached to the amine function. The latter chemical is a principal metabolic product in both animals and man.

In humans and test animals, arbutamine is very extensively degraded. Arbutamine is extensively metabolized in humans, and only 10 percent of the dose is recovered as intact arbutamine in the urine. The major metabolites of arbutamine identified in the urine were water soluble glucuronide conjugates of methoxyarbutamine and 2-keto arbutamine which accounted for 64% and 30%, respectively, of the total urinary ^{14}C activity. Metabolism proceeds via catechol-O-methyltransferase, monoamine oxidase beta and glucuronidation.

7.2.8 Probable Fate of Arbutamine and Its Metabolites

The processes that affect the environmental fate of arbutamine are summarized in Appendix A. Based on (1) the extensive breakdown of arbutamine before it is eliminated and (2) the ease with which arbutamine undergoes photodegradation, arbutamine and its principal metabolites are unlikely to survive sewage treatment. The small amounts that may be released in effluent, moreover, can be expected to be degraded by the pathways that degrade catecholamine synthesized by animals.

7.3 SOIL

Arbutamine will be deposited in landfills with the solid wastes of product formulation and unused, returned goods. If sewage plant sludge from the North Shore Sanitary District and is landfilled, arbutamine may also be deposited as an adsorbate to the sludge. Biodegradation is the expected fate in landfills.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

If the new product is approved, no adverse environmental effects are expected. From Subsection 6.6.1, the worst-case, combined concentration of arbutamine and its metabolites at typical wastewater treatment plants in year 2000 from use of products that contain it could range from 0.06 ng/L to 0.13 ng/L. The typical worst-case concentration in surface water would be 0.13 pg/L. These concentrations are calculated as if human metabolism and microbial biodegradation did not occur. However, as pointed out in Item 7 (Subsection 7.2.7), human metabolism is extensive and microbial degradation of similar substances is readily achieved. Therefore, the amounts of arbutamine and its metabolites that would actually be released are negligible compared to the continuing release of similar chemicals biosynthetically produced by indigenous animals.

Animal studies in dogs, rabbits, rats and mice have shown toxicity in line with the cardiovascular changes associated with the phenomenon of selective ischemia of the ventricular papillary myocardium when given intravenously or subcutaneously. The oral bioavailability of arbutamine is less than 10 % in rats. Arbutamine was not found to be a primary skin irritant when tested on intact or abraded rabbit skin. In rabbit teratology studies, Arbutamine produced no changes in any of the reproductive or fetal parameters examined, and was considered non-mutagenic in the Ames Bacterial Reverse Mutation Assay and the Mouse Micronucleus Test.

9. USE OF RESOURCES AND ENERGY

The proposed action does not require a large commitment of resources. Moreover, no irreversible or irretrievable commitment of limited national resources will be involved.

Synthesis of the arbutamine at facility and preparation of the product at Gensia's Irvine facility will be a minor activity that will not affect the power consumption required to maintain operations. Production activities would be scheduled to fit within the efficient operation of the facility. No addition capacity expansion is required at either facility for arbutamine production.

As discussed in Item 8, the environmental impact of releases from manufacturing and use of this product is negligible. Therefore, it is unlikely that threatened or endangered species could be affected.

The State of does not regard property in the vicinity of facilities to have historical or archaeological importance (Appendix D). The State of California does not regard property in the vicinity of Gensia's Irvine facility to have historical or archaeological importance (Appendix D). Moreover, no expansion of these facilities is necessary for this new products.

10. MITIGATION MEASURES

Compliance of the proposed action with applicable emission requirements is provided in Appendix E. Material Safety Data Sheets are provided in Appendix F. Unused vials (past the labeled expiration date) will be returned to Gensia Laboratories for disposal. Waste minimization studies are an ongoing activity at facilities. As their results become available, practical measures to increase control of wastes are incorporated into manufacturing procedures. Minimization of waste increases profitability and, therefore, receives substantial attention.

11. ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental impacts have been identified for the proposed action. The drug substance, arbutamine, is extensively metabolized in humans. Manufacturing releases should be readily photodegraded or biodegraded, after acclimation of the sludge culture. Furthermore, estimates of worst-case concentrations of arbutamine in surface waters (from its release without biodegradation) are far below the concentrations that produce toxic effects.

Because no adverse environmental impact is expected, alternatives to the proposed action are not being considered. If this new product is not approved (as a no-action alternative), patients for whom exercise is not possible may not be receive appropriate cardiovascular therapy.

12. PREPARER

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The preparer's resume is provided at the end of Item 15.

13. CERTIFICATION

The undersigned certifies that the information provided to N.W. Gabel & Assoc. (preparer) by Gensia Inc. (applicant) is true and accurate to the best of our knowledge.

Signature Ernst Kurt Metzner **Date** 8/7/95
Title Scientific Investigator

The undersigned certifies that the information presented herein is true, accurate, and as complete as provided to N.W. Gabel & Assoc. for preparation in accordance with 21 CFR 25.31(a).

Signature Ernst Kurt Metzner **Date** 8/7/95
Title Scientific Investigator

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* Dr. Gabel compiled this Environmental Assessment in large part, with Kurt Metzner, before March 1995. He is recently deceased, no signature for Dr. Gabel will be provided.

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Summary of Environmental transport and Fate of Arbutamine

Environmental Process	Summary Statement	Confidence of Data*
Photolysis	This substance absorbs radiation in the wavelength range of terrestrial sunlight. Photolysis of arbutamine will proceed with a half-life of about 1.2 days in surface water.	High
Oxidation	Oxidation of arbutamine probably proceeds with a half-life of about 3 days at pH 7 in the absence of sunlight.	High
Hydrolysis	This process is not relevant for arbutamine or its metabolites.	High
Volatilization	Arbutamine will not volatilize to the atmosphere from water or soil because it will be a salt in the ambient environment.	High
Sorption/Desorption	Arbutamine probably can absorb to sediment and sludge.	Low
Bioaccumulation/ Bioconcentration	Elimination of polar metabolites precludes bioconcentration in aquatic and terrestrial organisms	High
Biodegradation	Arbutamine is extensively metabolized before elimination and should also be readily degraded by environmental microorganisms	High

*Levels of confidence are based on criteria discussed in USEPA (1979). High confidence requires that the data are quantitative; rates constants and half-lives are either explicitly described or can be calculated from the results. Medium confidence is assigned to quantitative data reported for a different but structurally related compound. A low confidence ranking is given to theoretical estimates or to speculative statements.

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