NDA19-908

E.A.

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# ENVIRONMENTAL ASSESSMENT

# AND

# FINDING OF NO SIGNIFICANT IMPACT

# FOR

# AMBIEM (zolpidem tartrate)

# TABLETS (5&10 mg)

## NDA 19-908

## FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

**FINDING OF NO SIGNIFICANT IMPACT**

**NDA 19-908**

**AMBIEN (zolpidem tartrate)**

**TABLETS (5 & 10 mg)**

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.

Ambien is a non-benzodiazepine hypnotic of the imidazopyrine class indicated for the treatment of transient, short-term, and chronic insomnia. Chemically, Ambien is N, N, 6-triethyl-2-p-tolyl-imidazo[1,2-a]pyridine-3-acetamide L-(+)-tartrate (2:1).

The water solubility of Ambien is 23 mg/ml. The n-Octanol:water partition coefficient is 263 and the log $K_{ow}$ is 2.42. Ambien has a $K_{oc}$ range of 17-494 and a bioconcentration factor (BCF) of 2-33.

In support of their new drug application for Ambien tablets, Lorex Pharmaceuticals has conducted a number of environmental studies and prepared an environmental assessment (21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

The bulk drug substance is manufactured in France. The firm has provided a letter from the French environmental authority certifying that the manufacturing establishment is in compliance with applicable environmental regulation. The pharmaceutical dosage form is manufactured in Puerto Rico. A letter of certification of compliance with environmental regulation at this site is provided. The firm has described the controls exercised for hazardous and non-hazardous wastes. Occupational safety has been appropriately addressed and a Material Safety Data Sheet (MSDS) is attached as appendix E.

Ambien slowly hydrolysis and is rapidly photodegraded. Ambien is moderately biodegraded and is not inhibitory to sludge microorganisms. Ambien is relatively non-toxic to Daphia magna, rainbow trout, and Selenastrum.

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. Any residues of Ambien or its major metabolites entering the environment as a result of administering the drug to humans are expected to rapidly degrade.

DEC 18 1992

DATE

Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

12/15/92

DATE

Charles S. Kumkumian, Ph. D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: Environmental assessment
MSDS
FPL

# Environmental Assessment

# for the Manufacture of

# Zolpidem Tartrate

# ([redacted] Tablets)

AMBIEN

February 28, 1991

Lorex Pharmaceuticals

21 CFR 314.50 (d)(1)(iii)

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# Environmental Assessment

## Zolpidem Tartrate

## 21 CFR 314.50 (d)(1)(iii)

1. **Date:** February 28, 1991

2. **Name of Applicant:** Lorex Pharmaceuticals

3. **Address:** 4930 Oakton Street
Skokie, Illinois 60077

4. **Description of Proposed Action:**
Under the provisions of 21 CFR 25.31a, an environmental assessment must be prepared for proposed approvals of products regulated by the Food and Drug Administration (FDA). This environmental assessment (EA) provides sufficient information for the FDA to make a determination for either (1) a finding of no significant impact (FONSI) or (2) that an Environmental Impact Statement is required before agency approval can be given. This EA addresses issues regarding the manufacturing of the bulk chemical and the drug dosage form, the use and disposal of the active ingredient by the patient, and the occupational safety of the manufacturing processes. The information will be summarized to show that neither human health nor the environment will be adversely affected by approving the manufacture and sale of the bulk chemical substance, zolpidem tartrate, and the drug dosage form, [redacted]™ Tablets, throughout North America for the treatment of insomnia.

The bulk drug, zolpidem tartrate, will be manufactured in France by:

Synthelabo Pharmacie
BP 30 ZI de Mourenx Route d'Artix
64150 Mourenx France

The pharmaceutical dosage form, [redacted] Tablets, will be manufactured in Puerto Rico by:

Searle & Co.
Carr, 189, KM. 2.0
Caguas, Puerto Rico 00936

**5. Identification of Chemical Substances that are the Subject of the Proposed Action:**

**Chemical Name:** Zolpidem Tartrate

(1) N,N,6-trimethyl-2-p-tolyl-imidazo [1,2-a]pyridine-3-acetamide L-(+)-tartrate (2:1)

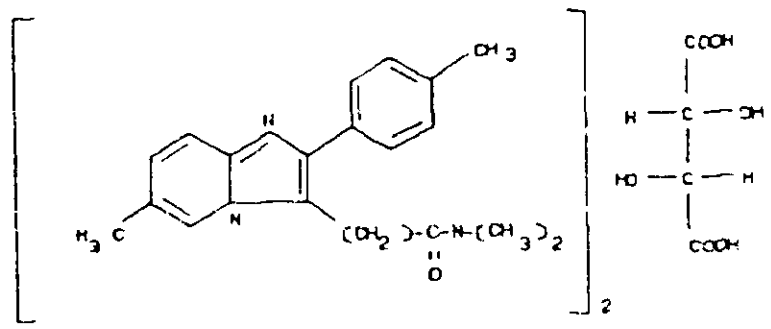
**CAS Registration Number:** 99294-93-6

**Code Designation:** SL 80.0750-23N (Synthelabo)

**Molecular Weight:** 764.88

**Molecular Formula:** $(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$ or $C_{42}H_{48}N_6O_8$

**Structural Formula:** Zolpidem Tartrate



**Physical Description:** Zolpidem tartrate is a white to off-white, odorless, microcrystalline powder.

**Additives and Impurities:**
The components of the [redacted] tablet formulation are:

Zolpidem tartrate
Lactose
Microcrystalline cellulose
Sodium starch glycolate
Hydroxypropyl methylcellulose 2910
Magnesium stearate
Purified water
Red dye number 40 (5 mg tablet only)

The components of the film-coating for the [redacted] tablets are:

Hydroxypropyl methylcellulose 2910
Opadry Y-1-7000 (titanium dioxide suspension)
Opadry YS-1-1418 (5 mg tablet only)
Polyethylene glycol 400
Purified water

6. **Introduction of Substances into the Environment:**

**Bulk Chemical Manufacturing:**
**Site Description:** The zolpidem tartrate bulk chemical active ingredient is manufactured in Mourenx, France by Synthelabo Pharmacie. The facility is located in a zoned industrial complex in a rural area of Mourenx. The manufacturing facility is unenclosed and open to the atmosphere allowing for good ventilation.

**Environmental Controls:** Air emissions are controlled by scrubbing and condensing units to ensure that acid and volatile emissions to the atmosphere are minimized. Hazardous wastes are segregated and stored onsite. Each month, these wastes are shipped offsite for disposal at an approved landfill permitted by the French authorities. Non-hazardous solid wastes are also segregated and shipped offsite to an approved landfill operation. Non-hazardous wastewaters are pH adjusted and pumped to a government permitted empty gas cavern 400 to 4,000 meters below the surface of the earth.

**Compliance Certification:** Table 1 summarizes the environmental matrix within which Synthelabo Pharmacie operates. Air, water, hazardous waste and solid waste are all administered by national regulations and regulatory agencies. Appendix A contains a letter from the regulatory authority in the French government certifying compliance of Synthelabo Pharmacie with all national and local environmental regulations.

Table 1. Regulatory Matrix for the Mourenx, France Plant.

| Environmental Regulatory Agency |
|---|
| Prefecture of the Department of Pyrenees-Atlantiques<br>Direction of Local and the Environment<br>Bureau of the Environment and Cultural Affairs<br>64021 Pau Cedex<br>France |
| Environmental Legislation for Air, Water, Hazardous and Solid Wastes |
| Air, Hazardous Waste, Solid Waste<br><br>Application Of Law 76/663, July, 1976<br>Installation for Protection of the Environment<br><br>Wastewater<br><br>.Law 64/1245 December 16, 1964<br>Administration and Distribution of Water and the Campaign Against Pollution |

**Drug Dosage Form Manufacturing:**

**Site Description:** The drug dosage form of Stilnox will be manufactured in Caguas, Puerto Rico. The Searle pharmaceutical plant is located in an area zoned for light industry. Three sides of the plant

are adjacent to roads and small commercial businesses. The fourth side of the facility borders residential housing.

**Description of Manufacturing Operations:** Appendix C contains a report from Stanley Consultants, Inc. outlining the process for manufacturing the dosage form of the Stilnox Tablets. One important aspect of plant operations involves the application of procedures that minimize or eliminate the generation of waste materials. Efforts to keep waste generation to a minimum involve the following administrative practices at the Caguas plant:

- Use of lined, closed containers for transporting dry materials throughout the facility to reduce particulate emissions.
- Vacuum loading of non-active ingredients into the processing equipment to reduce fugitive air emissions.
- Overpacking and disposal of container liners to reduce fugitive air emissions.
- Manual and vacuum cleaning of equipment before washing with water to reduce water emissions.
- Maximum use of disposable wipes to reduce water emissions.
- Use of disposable tray liners for drying operations to reduce water emissions.

**Overview of the Environmental Controls:** Puerto Rico operates under federal USEPA regulations (Region II). Air pollution controls focus on minimizing the emissions of particulate matter to the atmosphere. In Caguas, baghouse filter operations are utilized to capture in excess of 99 percent of the particulates leaving the tablet manufacturing and packaging operations. Hazardous wastes are segregated onsite and stored in a RCRA Part B permitted storage facility. All other pharmaceutical hazardous wastes are destroyed onsite in the permitted incinerator. Residual ash

from the incinerator is containerized and shipped offsite for disposal in a local approved landfill. Liquid hazardous wastes, lab packs and other hazardous non-combustible materials are shipped offsite to Safety Kleen, Inc. for final treatment and disposal at one of their approved facilities. Non-hazardous solid wastes are segregated and shipped offsite for disposal at approved local landfill facilities. Rejected and out-of-date pharmaceutical dosage products manufactured at Caguas are incinerated onsite. All labels, instruction inserts and non-pharmaceutical wastes are shredded and shipped for disposal to the approved municipal landfill. Non-hazardous wastewaters are treated in the onsite sequential batch reactor (SBR) biological activated sludge wastewater treatment facility. The effluent from this fill and draw operation is sewered directly to the Caguas POTW for further biological treatment in their trickling filter operations.

**Air:** Two separate exhaust systems are utilized at the Caguas facility to control airborne particulate emissions. The central dilution exhaust is a general system that collects particulates from local exhaust vents in the processing and packaging rooms. The exhausted air is passed to the atmosphere through a baghouse which has a removal efficiency of 99.9%.

The second exhaust system is a vacuum operation that is used during equipment cleaning and material transfer operations. Because of the quantity of the particles captured by the vacuum system, the air is subjected to three levels of treatment: a cyclone separator, baghouse, and HEPA filters connected in series. The cyclone separator is introduced up front to maintain the high capture efficiencies of the subsequent baghouse and HEPA filter operations. HEPA filters provide an additional removal efficiency in excess of 99.97% for particles larger than or equal to 0.3 microns.

From a mass balance determination found in

Appendix C, it is estimated that 3.0% of the active ingredient charged to the processing equipment was captured by the various air filtration systems (2.7 percent by the vacuum system and 0.3 percent by the central dilution exhaust system). The total quantity of zolpidem tartrate released to the atmosphere is conservatively estimated to be 38.5 mg per 150 Kg batch of manufactured 10 mg tablets. The Stanley Report (Appendix C) contains the details of these calculations.

**Water:** Wastewater is treated in the onsite sequential batch reactor (SBR) wastewater treatment plant which is designed to handle flows up to 130,000 gpd. Each of the two SBR vessels handle upto 85,000 gallons of waste per aeration sequence. Waste sludge is aerobically digested and disposed offsite in a regulated landfill. The major source of zolpidem tartrate in the wastewater results from equipment cleaning, primarily the Zanchetta granulator. Studies were conducted at the Caguas facility to quantify the potential release of zolpidem tartrate to the wastewater treatment plant (Appendix C). The results of the study indicate that 53.7 gm of zolpidem tartrate remained in the equipment after processing two CBI batches of the dosage product. The Caguas plant will generally manufacture one CBI batch per day and currently has a wastewater sewer flow from all industrial operations of 50,000 gallons per day. This equates to a maximum concentration of CBI or CBI of zolpidem tartrate in the influent wastewater entering the SBR at the manufacturing plant. Following biological treatment in the onsite SBR, the effluent is clarified and discharged to the Caguas POTW trickling filter plant.

**Solid Wastes:** Solid wastes are collected at various stages of [redacted] tablet production. These include the disposable liners, air pollution control filters, off-spec and damaged packaging materials. The collected



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wastes are stored, shredded and destroyed in the Searle onsite incinerator.

**Occupational Exposure:** Occupational exposure of employees to Zolpidem Tartrate is managed by established work practices and occupational controls. Where there is a potential for exposure, employees are required to use personal protective equipment including safety glasses or goggles, gloves, dust masks or respirators and long sleeve shirts as specified in the Material Safety Data Sheet (Appendix E).

**Compliance Certification:** Table 2 summarizes the environmental matrix within which the Caguas plant operates. Included are the names of the US and Puerto Rico regulatory legislation and enforcement agencies responsible for controlling emissions and discharges of hazardous and non-hazardous wastes to the appropriate environmental compartments. Appendix B contains letters certifying compliance of the Searle pharmaceutical plant with all federal and local environmental regulations.

7. **Fate of Emitted Substances in the Environment:** Table 3 summarizes the physical/chemical properties of zolpidem tartrate used to determine the fate and partitioning of the zolpidem tartrate compound upon release to the environment.

   At the concentration that zolpidem tartrate is expected to exist in the environment, the solubility, the n-octanol/ water partition coefficient, the bioconcentration factor and the soil adsorption coefficient indicate that zolpidem tartrate is a water soluble compound that is not likely to bioconcentrate or sorb onto soil or organic particles. The environmental interpretations used to support these conclusions are summarized in Table 4.

   In Table 5, the rates at which zolpidem tartrate will hydrolyze, photolyze, and biodegrade in the environment are summarized. Hydrolysis of zolpidem tartrate is moderately slow with only 50% hydrolyzed at 80°C after 6 months. In the presence of daylight zolpidem tartrate is

Table 2. Regulatory Matrix for Caguas, Puerto Rico Plant.

| Matrix | Agency | Permit Number |
|---|---|---|
| Air | Junta de Calidad Ambiental<br>Box 11488<br>Santurce, Puerto Rico<br>00910 | PFE 13-080733-<br>I-II-III-0 |
| Waste Water | P.R.A.S.A.<br>P.O. Box 7066<br>Barrio Obrero Station<br>San Juan, Puerto Rico<br>00916 | GDA-88-602-004 |
| Hazardous and Solid Wastes | U.S. EPA, Region II<br>Jacob Javits Fed. Bldg.<br>New York, New York<br>10278 | PRD090378225 |

rapidly photolyzed with 35% degradation after one month. Upon release of zolpidem tartrate to the atmosphere, upper layers of surface water or to the terrestrial environmental compartments, the drug substance would be exposed to sunlight and to degradation by photolysis. In a study conducted by [redacted] Laboratories (Appendix D-5), approximately 30% of the compound was biodegraded after 28 days using recycled activated sludge as the source of the biological seed. Zolpidem tartrate should be biodegradable by the general microorganisms found in aquatic and terrestrial environments, including those concentrated and maintained in biological wastewater treatment plants. Results of the microtox test (Appendix D-1) indicate that zolpidem tartrate is neither inhibitory nor toxic to the activated sludge microorganisms at the ppb level.

Based on the demonstration of zolpidem tartrate to undergo degradation by hydrolysis, photolysis and biological mechanisms, the compound will be nonpersistent in the environment and will not accumulate to levels capable of causing toxic effects to human health or to the environment.

**Table 3. Physical/Chemical Properties of Zolpidem Tartrate.**

| PROPERTY | VALUE | REFERENCE |
|---|---|---|
| Water Solubility: | 23 mg/ml @ 20°C | (1) |
| n-Octanol/Water Partition Coefficient ($K_{ow}$): | 263 @ pH=7.4 | (7) |
| Log $K_{ow}$: | 2.42 @ pH=7.4 | |
| Soil Absorption Coefficient ($K_{oc}$): | 17.4 - 493.7* | (2) |
| Log $K_{oc}$: | 1.24 - 2.69 | |
| Bioconcentration Factor (BCF): | 2.1 - 32.5* | (2) |
| Log BCF: | 0.33 - 1.51 | |
| Melting Point: | 193 - 197°C | (7) |
| Molecular Weight: | 764.88 | (7) |
| Molecular Formula: | $C_{42}H_{48}N_6O_8$ | (7) |

* Values were calculated from equations in Reference 2.

**Table 4. Environmental Interpretation of Physical/Chemical Data (Reference 2).**

| PARAMETER | ENVIRONMENTAL INTERPRETATION |
|---|---|
| Water Solubility: | Soluble compounds are more readily biodegradable than insoluble compounds, tend to have relatively low adsorption coefficients for soils and sediments. |
| n-Octanol/Water Partition Coefficient ($K_{ow}$): | |
| $K_{ow}$<10 | Chemicals are not expected to significantly bioconcentrate or sorb onto organic particles. |
| $K_{ow}$>10,000 | Chemicals may bioaccumulate or sorb significantly. |
| Soil Absorption Coefficient ($K_{oc}$): | |
| $K_{oc}$>1000 | Chemicals are highly sorbed to the organic matter in the soil. |
| $K_{oc}$<100 | Chemicals are considered to be moderately to highly mobile. |

8. **Environmental Effects of Released Substances:**
Lorex Pharmaceuticals expects to market the following quantities of zolpidem tartrate in both the U.S. and Canadian marketplaces:

**Table 5. Environmental Fate of Zolpidem Tartrate.**

**Mechanism:**

Hydrolysis:

| pH | Half-Life (months) | Temperature (°C) |
|---|---|---|
| 2.2 | 25.4 | 80 |
| 3.0 | 102.5 | 80 |
| 4.0 | 12.7 | 80 |
| 5.0 | 5.5 | 80 |
| 6.0 | 20.8 | 80 |
| 7.0 | 6.1 | 80 |
| 8.0 | 32.8 | 80 |

Summary: 50% hydrolyzed at 80°C after 6.1 months (Reference 5)

Photolysis:

Summary: An aqueous solution exposed to daylight for one month showed 35% degradation (Reference 5)

Microtox:

Summary: Using activated sludge, the $EC_{50}$ of zolpidem tartrate is 2900 mg/L. (Appendix D-1).

Biodegradation:

Summary: Zolpidem tartrate was observed to degrade 26.3 - 33.3 percent after 28 days. (Appendix D-5)

Table 6. Projected Sales Forecast for Zolpidem Tartrate.

| YEAR | United States Sales | Canadian Sales |
|---|---|---|
| 1991 | C B I | |
| 1992 | | |
| 1993 | | |
| 1994 | | |
| 1995 | | |

Over the next five years, the highest annual production of zolpidem tartrate is CBI in the United States and CBI in Canada or a total production of CBI . A conservative estimate of the maximum expected environmental concentration entering a wastewater treatment plant is calculated to be CBI or CBI . This assumes that all of the zolpidem tartrate is directly discharged as parent compound into the sewer by patients using the product; a combined U.S. and Canada population of 275 million people; and an estimated daily water usage rate of 135 gallons/person/day.

Based on the definition of toxicity in 21 CFR Part 25.15, a substance is considered toxic in the environment if the maximum concentration of the substance at any point in the environment exceeds the concentration of the substance that causes any adverse effect in a test organism species (minimum effect level) or exceed 1/100$^{th}$ of the concentration that causes 50% mortality in a test organism species, whichever concentration is less. The toxicological data for zolpidem tartrate is summarized in Table 7.

Using the most conservative $EC_{50}$ value from Table 7 of 2.2 mg/L for algae, the concentration where zolpidem tartrate would have toxic effects is 0.022 mg/L or 22 ppb or 22,000 ppt. Comparing the maximum expected environmental concentration of 21 ppt to the estimated toxicity value

**Table 7. Environmental Effects of Zolpidem Tartrate.**

| MATRIX | TEST | $EC_{50}$ (mg/L) | NOEC (mg/I) |
|---|---|---|---|
| Biological | Microtoxicity | 2900 | ----- |
| Invertebrate | Daphnia magna | 120 | 16 |
| Vertebrate | Rainbow trout | 22 | 6.2 |
| Algae | Selenastrum | 2.2 | 0.32 |

that could have an adverse impact on human health and the environment of 22,000 ppt gives a safety factor in excess of 1,000 using the Lorex Pharmaceutical five year production estimates. Based on the available toxicological information, production of zolpidem tartrate would have to be increased to 1.1 million Kg before a toxic effect on human health or the environment could occur. This value also assumes that none of the zolpidem tartrate is removed from the environment by the biodegradation, hydrolysis, and photolysis degradation mechanisms.

Table 8 lists the by-products known to be generated from the metabolic, hydrolytic, and photodegradative mechanisms. During metabolism, zolpidem tartrate is converted to inactive metabolites by oxidation and hydroxylation. In a study of three patients, < 1% zolpidem tartrate was excreted in the urine as parent material (Reference 5). Using radiolabeled parent, 99% of the dose was excreted as inactive metabolites (48 to 67% in the urine and 29 to 42% in the feces). In general, the metabolic compounds from all routes of degradation are more polar than the zolpidem tartrate parent compound thus indicating that they should be readily subject to the biodegradation mechanisms found in the activated sludge process of community POTW's.

**Table 8. Degradation By-products of Zolpidem Tartrate**

| | |
|---|---|
| Metabolism | Hydroxylated Zolpidem<br>SL 84.0589<br>SL 84.0853<br>(Reference 6) |
| Photolysis | -N,N,6-trimetnyl-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-(2-oxoacetamide)<br>-6-Methyl-2-(4-methylphenyl)imidazo [1,2-a]pyridine-3-carboxaldehyde<br>-5-Methyl-2-(4-methylbenzamido)pyridine |
| Hydrolysis | N,N,6-trimethyl-2-(4-methylphenyl) imidazo[1,2-1]pyridine-3-acetic acid |

**9. Use of Resources and Energy:**
The primary natural resources utilized for production of [redacted] tablets will be the electricity, propane, and fuel oil utilized during drug manufacture. Estimates of daily usage at the bulk drug manufacturing facility in France and the dosage packaging facility in Puerto Rico are summarized in Table 9.

**10. Mitigation Measures:**
No adverse environmental impacts are expected from the proposed action.

**11. Alternatives to Proposed Action:**
No adverse environmental impacts are expected from the proposed action.

Table 9. Projected Natural Resource Use Related to Manufacture of [redacted] Tablets U.S.P.

| LOCATION/USE | ELECTRICITY (kwh/day) | PROPANE (gal/day) | STEAM (kwh/day) |
|---|---|---|---|
| Mourenx, France: Total Daily Usage | | | |
| [redacted] as Percent of Manufacturing | | | |
| [redacted] Energy Usage | CBI | | |
| Caguas, Puerto Rico Total Daily Usage | | | |
| [redacted] as Percent of Manufacturing | | | |
| [redacted] Energy Usage | | | |

*OIL = (gals/day)

**12. List of Preparers:**

Name: Jane T. Red
Employer: Young-Morgan & Assoc.
Qualifications:
M.S. in Hydrology

Eight years of experience in environmental consulting projects including fate and transport assessments.

Name: Daniel E. Sullivan
Employer: G.D. Searle & Co.
Qualifications:
Ph.D. in Environmental Engineering

Twelve years of experience in chemical fate and effect evaluations, plant operations and regulatory compliance.



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Environmental Assessment
Zolpidem Tartrate

Name: Glenn R. Gabriel
Employer: G.D. Searle & Co.
Qualifications:
M.S. in Chemical Engineering

Ten years experience in pollution control, safety and environmental engineering.

**13. Certification:**
The undersigned certifies that the information presented is true, accurate and complete to the best knowledge of G.D. Searle & Co.:

Date: March 13, 1991

Signature: Donald S Nurnberg

Name: Donald S. Nurnberg, P.E.

Title: Sr. Director, Safety and Environmental Affairs

**14. References:**

(1) Budavari, S. (editor). 1989. The Merck Index. Eleventh Edition. Merck & Co., Inc. Rahway, N.J.

(2) Hoffman, B.L. and J.C. Matheson. 1987. Environmental Assessment Technical Assistance Handbook. NTIS Publication No. PB87-175345.

(3). K. Verschueren. 1983. Handbook of Environmental Data on Organic Chemicals. Van Nostrand Reinhold Company, New York.

(4). Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1990. Handbook of Chemical Property Estimation Methods. American Chemical Society, Washington, D.C.

(5). Zolpidem IND 25,361 filed Nov. 15, 1984, pg. 76.

(6). Zolpidem Tartrate NDA No. 19-908 filed Jan. 26, 1989, vol. 034, pg. 0036.

(7). Zolpidem Tartrate NDA No. 19-908 filed Jan. 26, 1989, vol. 002, pg. 0006-0007.

Appendix A

Bulk Drug Manufacturing Plant
Certification of Environmental Compliance

**DIRECTION
DES COLLECTIVITÉS LOCALES
ET DE L'ENVIRONNEMENT**

BUREAU DE L'ENVIRONNEMENT
ET DES AFFAIRES
CULTURELLES

**64021 PAU CEDEX**
**Tél. 59 27 60 00** poste 3755
**Télex n° 570818**

*Référence à rappeler dans toute correspondance 3e Bureau*

EG/AL

PAU, le 19 décembre 1990

# ATTESTATION DE CONFORMITE D'INSTALLATIONS CLASSEES POUR LA PROTECTION DE L'ENVIRONNEMENT

-*-

LE PREFET des PYRENEES-ATLANTIQUES,

ATTESTE que la société SYNTHELABO-PHARMACIE, dont le siège social est 58, rue de la Glacière à PARIS, est autorisée à exploiter une usine de fabrication de produits pharmaceutiques, située sur la plate-forme SOBEGI à MOURENX.

Les conditions d'exploitation de l'usine au regard de la protection de l'environnement, en particulier dans le domaine des risques industriels, de l'eau, de l'air et des déchets, sont précisées dans les arrêtés préfectoraux N° 89/IC/264, 89/IC/265 et 89/IC/266 du 30 novembre 1989 pris en application de la loi N° 76-663 du 19 juillet 1976 relative aux installations classées pour la protection de l'environnement et de la loi N° 64-1245 du 16 décembre 1964 relative au régime et à la répartition des eaux et à la lutte contre leur pollution.

Le fonctionnement des installations n'a pas donné lieu, à ce jour, à observation particulière de la part des services d'inspection.

LE PREFET,

*Pour le Préfet*
*et par délégation*
*Le Directeur*

**Evelyne BELLANGER**

ENGLISH TRANSLATION

020

PREFECTURE OF THE DEPARTMENT OF PYRENEES-ATLANTIQUES

FRENCH REPUBLIC

DIRECTION OF LOCAL
AND THE ENVIRONMENT

PAU, December 19th 1990

BUREAU OF THE ENVIRONMENT
AND CULTURAL AFFAIRS

64021 PAU CEDEX
Tel. 59 27 60 00
Extension: 3755
Telex n° 570818

BG/RZ/JA1991(D1)

CERTIFICATE OF CONFORMITY

FOR INSTALLATIONS CLASSED

FOR ENVIRONMENTAL PROTECTION

The PREFECT of the Department of PYRENNEES-ATLANTIQUES,

CERTIFIES that the SYNTHELABO PHARMACIE Company, whose registered office is located at 58 rue de la Glacière, in PARIS, is authorized to operate a plant which manufactures pharmaceutical products, located on the SOBEGI industrial site at MOURENX (France).

The operating conditions of this plant with regards to the protection of the environment, in particular in the domaine of industrial risks, of water and of waste material are pricesly defined in the Departmental order n° 89/IC/264, 89/IC/265, and 89/IC/266 of November 30, 1989 in application of the law n° 76-663 of July 19, 1976 relative to installations classed for the protection of the environment and of law n° 64-1245 of December 16, 1964 relative to the administration and distribution of water and the compaign against pollution.

The functionning of these installations have not given, just to this day, any particular observation from our inspection services.

THE PREFECT,

For the Prefect
and by delegation
The Director

Evel ne BELLANGER

Environmental Assessment
Zolpidem Tartrate

Appendix B

Dosage Form Manufacturing Plant
Certification of Environmental Compliance

February 22, 1991

Dr. Daniel E. Sullivan
Manager, Environmental Affairs
G.D. Searle & Co.
5200 Old Orchard Road
Skokie, Illinois, USA 60077

RE: CERTIFY COMPLIANCE WITH
ENVIRONMENTAL REGULATIONS

**SEARLE**

Dear Dr. Sullivan:

I certify that Searle, Caguas Plant, located at Road #189, Km. 2.0, Caguas, Puerto Rico 00625 is in full compliance with all air, solid waste, hazardous waste and wastewater regulations that have been promulgated by appropriate national and local government authorities. I also certify that we are in compliance with all required occupational regulations governing the safety of the workforce responsible for the manufacturing, handling and packaging of Searle products.

Sincerely,

Daniel Lebrón
President & General Manager
0355J-59

Environmental Assessment
Zolpidem Tartrate

Appendix C

Report on Estimated Waste Generation from Zolpidem Dosage Manufacture

30-252

APPENDIX C, D [redacted] (PAGES [redacted] - [redacted] OMITTED

CONFIDENTIAL BUSINESS INFORMATION

# Appendix E

## Material Safety Data Sheet for Zolpidem Tartrate

July 9, 1990

SYNTHELABO PHARMACIE
MATERIAL SAFETY DATA SHEET

**MATERIAL**

Zolpidem Tartrate

**CHEMICAL NAME**

N,N,6-Trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acteamide L-(+)-tartarate **OR**
N,N,6-Trimethyl-2-p-tolylimidazo[1,2-a]pyridine-3-acetamide L-(+)-tartarate

**CHEMICAL FORMULA**

$(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$

**CAS NUMBER**

99294-93-6

**SYNONYMS**

SL80.0750-23N

**PERMISSIBLE EXPOSURE**

OSHA PEL: Not established
ACGIH TLV: Not established
Searle A.C.O.: Not established
Therapeutic Dosage: 5-15 mg/day
Toxicity: Carcinogenicity: Negative in rats and mice

Reproductive Toxicity: Negative in rats and rabbits

Teratogenicity: Negative in rats and rabbits

Mutagenicity: Negative in the Ames, the micronucleus and mouse lymphoma tests.

General: Oral Rat $LD_{50}$ male: 695 mg/kg

female: 1030 mg/kg

In chronic toxicity studies (52 weeks) in rats and monkeys dosages as low as 5 mg/kg produced CNS depression, but no other signs of toxicity. These were considered to be pharmacologic not toxicologic effects.

Dermal and occular irritancy, and delayed contact sensitization have not been determined.

**PHYSICAL DESCRIPTION:**

PHYSICAL STATE: Solid powder
APPEARANCE: White, hygroscopic, microcrystalline powder
ODOR: None
TASTE: Not available
DENSITY: Not available
MOLECULAR WEIGHT: 764.88
BOILING POINT AT 1 ATM,F: Not applicable
SOLUBILITY IN WATER, MG/ML WATER AT 20C: 23
FLASH POINT, CLOSED CUP, F (OR OPEN CUP IF OC): Not applicable
VAPOR PRESSURE AT 20C MM HG: Not applicable
MELTING POINT, C: 193-197C
UPPER EXPLOSIVE LIMIT IN AIR, % BY VOLUME: Not applicable
LOWER EXPLOSIVE LIMIT IN AIR, % BY VOLUME: Not applicable
MINIMUM EXPLOSIVE CONCENTRATION IN AIR: 10 $g/m^3$
SEVERITY RATING: Very readily flammable. ALL PROCESS EQUIPMENT NEEDS TO BE GROUNDED. DO NOT TRANSFER MATERIAL THROUGH NON-CONDUCTIVE PIPES OR LINES. AVOID FORMATION OF DUST CLOUDS.
AUTOIGNITION TEMPERATURE: 420°C

**INCOMPATIBILITIES**

None reported

**STABILITY**

At least 3 years at room temperature without special precautions.

**PROTECTIVE EQUIPMENT REQUIREMENTS**

Degree of Exposure:

| | |
|---|---|
| Minor: | Safety glasses, rubber gloves, long sleeves, slacks, dust mask for materials having a TLV 0.05 $mg/m^3$. |
| Moderate: | Dust tight goggles, rubber gloves, long sleeves, slacks, HEPA respirator. |
| Gross: | Rubber gloves, long sleeves, slacks, disposable suit and full face supplied air respirator or air hood. |

**WEAR EYE PROTECTION TO PREVENT**

Dust from entering eyes

**EMPLOYEE SHOULD WASH**

Hands, face and any exposed skin which has been in contact with the powder should be washed abundantly with water. Shower at end of shift.

**WORK CLOTHING SHOULD BE CHANGED DAILY**

**REMOVE CLOTHING**

Upon contamination and at the end of each work shift.

**ROUTE OF ENTRY INTO BODY**

Eye, inhalation, oral

**CLINICAL END POINT**

To treat insomnia

**SYMPTOMS**

In clinical trials, oral dosages as low as 5 mg caused headache, drowsiness, dizziness, confusion, lightheadedness, lethargy, intoxicated feelings, ataxia, nausea, dyspepsia, vomiting, myalgia, amnesia, sinusitis, and pharyngitis.

Inhalation or ingestion of the product will give rise to symptoms of somnolence or sleep, confusion and tiredness.

**FIRST AID**

Route of Entry:

| | |
|---|---|
| Skin Contact: | Skin which has been in contact with the powder should be washed abundantly with water. Contact a doctor immediately if there is a skin problem. |
| Eyes: | Wash abundantly with water for at least 15 minutes. Contact a doctor immediately. |
| Inhalation: | Evacuate from the contaminated area. Watch closely and call a doctor immediately. |
| Ingestion: | Contact a doctor immediately. |

**TARGET ORGANS**

Central nervous system and gastrointestinal systems.

**SPECIAL PRECAUTIONS**

Individuals with signs or symptoms of depression, pulmonary insufficiency, impaired hepatic function should avoid contact unless medical clearance is given. If exposure results in symptoms (drowsy, dizzy, confused, lightheaded), individuals should avoid dangerous machinery.

**LEAK AND SPILL PROCEDURES**

Vacuum or sweep using wet methods. Collect waste for proper disposal.

**EXTINGUISHING MEDIA**

$CO_2$ or dry chemical

**WASTE DISPOSAL METHODS**

Incinerate or bury in an approved landfill.

**REGISTRY TOXIC CHEMICALS NUMBER**

For Futher Information Contact:

Lorex Pharmaceuticals
P.O. Box 163
4930 Oakton Street
Skokie, Illinois 60077

Phone: (708) 982-8445 or (708) 982-8400

002--0318

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# ENVIRONMENTAL ASSESSMENT

1. *Date:* December 20, 1988

2. *Name of Applicant/Petitioner:* Lorex Pharmaceuticals

3. *Address:* 4930 Oakton Street
P.O. Box 163
Skokie, Illinois 60077

4. *Description of the Proposed Action:*

The following environmental assessment report is prepared pursuant to 21 CFR 25.31a, covering the pharmaceutical manufacture of Stilnox™ (zolpidem tartrate) tablets. Stilnox is intended for use in humans for the treatment of insomnia and only by the order of licensed medical practitioners.

Approval is requested for the manufacture of the pharmaceutical dosage form (tablet), since the active ingredient, zolpidem tartrate, will be manufactured outside the U.S.

The tablets will be manufactured by:

The drug product will be distributed throughout

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

Chemical names: zolpidem tartrate
(1) N, N, 6-trimethyl-2-(4-methylphenyl)imidazo [1,2-a] pyridine-3-acetamide[R-(R* ,R*)]-2,3-dihydroxybutanedioate (2:1)
(2) N,N,6-trimethyl-2-p-tolylimidazo[1,2-a]pyridine-3-acetamide L-( + )-tartrate (2:1)

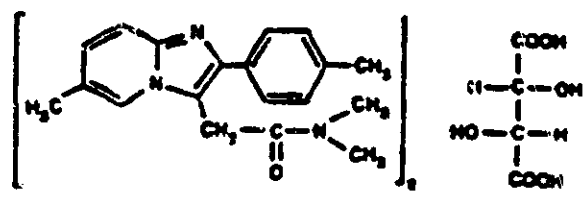
Code designation: SL 80.0750-23N

CAS Registry No.: 99294-93-6

Molecular formula: $(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$ or $C_{42}H_{48}N_6O_8$

Molecular Weight: 764.88

Structural formula:



Physical description: White to off-white odorless crystalline powder.

The components of the Stilnox tablet formulation are:

| | |
|---|---|
| Zolpidem tartrate | |
| Lactose | NF |
| Microcrystalline cellulose | NF |
| Sodium starch glycolate | NF |
| Hydroxypropyl methylcellulose | USP |
| Magnesium stearate | NF |
| | USP |

The components of the tablet's film-coating are:

| | |
|---|---|
| Hydroxypropyl methylcellulose | USP |
| Opaspray M-1-7111-B (titanium dioxide suspension) | |
| Polyethylene glycol | NF |
| | USP |

6. *Introduction of Substances into the Environment:*

This manufacturing process consists of the compounding of the above materials into an aqueous wet granulation and compression into a tablet dosage form, followed by aqueous film-coating. The expected emission into the environment of any substance is nil. All compounding operations are conducted in controlled environment areas and the negligible waste resultant is collected in self-contained dust collection units. Disposal of any such waste is conducted in accordance with Federal and local Puerto Rican EPA requirements for the disposal of hazardous materials.

7. *Fate of Emitted Substances in the Environment:*

a) air - Control of manufacturing operations (dust collection, waste collection, etc.) precludes potential of air pollution. Any solid waste including degradation products disposed via incineration will be nontoxic and in accordance with Federal and local statutory requirements.

b) freshwater, estuarine, and marine ecosystems - These substances will not pollute the water systems. The minimal volume of wastewater produced by production operations will be appropriately treated in licensed treatment facilities. Solvent waste will be collected and stored according to EPA regulations and transported via licensed waste haulers to permitted liquid waste reclamation sites.

c) terrestrial ecosystems -
Production operations or subsequent disposal of substances and any degradation products or packaging materials will not affect terrestrial ecosystems. Solid waste material, which meets appropriate standards of characterization and nontoxicity, may be appropriately disposed of in licensed land fills.

8. *Environmental Effects of Released Substances:*

The effect of any of the substances comprising Stilnox tablets upon any animals, plants, humans or other organisms as a consequence of the use or disposal of the drug product is negligible, other than the expected pharmacologic effect upon humans for which the drug is prescribed. Toxicological data on several animal species and safety studies on humans have established the safety of zolpidem for use in insomnia at much higher levels than can reasonably be expected to occur in the environment as a result of the proposed action, as noted in item 4 above. There is no anticipated pollution of the environment as a consequence of production or use (as stated above in item 7) and therefore the exposure of any ecosystem to this drug product is limited to its intended use as pharmaceutical therapy for humans.

9. *Uses of Resources and Energy:*

Stilnox tablets will be produced in at a pharmaceutical production facility located near which is already in operation as a pharmaceutical manufacturing plant. The only natural resource required for production is water from the city supply which is subjected to distillation and purification procedures to render it suitable for pharmaceutical production. The required energy resources for pharmaceutical production are not excessive and consist of power supplies to plant maintenance systems, heating/cooling, water, electrical, etc.

10. *Mitigation Measures:*

The production of Stilnox tablets will be conducted within a confined, controlled environment area with accumulation, isolation and safe disposal of all wastes generated.

11. *Alterations to the Proposed Action:*

No potential adverse environmental impact has been identified. There is neither benefit nor risk to the environment associated with the production of Stilnox tablets.

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PG. 4

12. *List of Preparers:*

Byron G. Scott, R.Ph. - 8 years experience in pharmaceutical regulatory affairs in private industry.

James A. Wachholz, B.S., MBA - 12 years experience in pharmaceutical QA/QC and regulatory compliance including responsibility for state and federal EPA compliance (domestic and Commonwealth of Puerto Rico).

13. *Certification:*

The undersigned certifies that the information presented is true, accurate and complete to the best of the knowledge of Lorex Pharmaceuticals.

Byron G. Scott

B. G. Scott, R.Ph.
Manager, Regulatory Affairs

BS/ic

PROPOSED CONTAINER LABEL

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Stilnox 10 mg Tablets

Bottle of 500 tablets