

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-692

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR

Serevent[®] (salmeterol xinafoate) Diskus[®]
Inhalation Powder

(salmeterol xinafoate)

INHALATION POWDER

NDA 20-692

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF PULMONARY DRUG PRODUCTS
(HFD-570)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-692

Serevent® (salmeterol xinafoate) Diskus® Inhalation Powder
(salmeterol xinafoate)

INHALATION POWDER

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 Serevent® (salmeterol xinafoate) Diskus® Inhalation Powder, Glaxo Wellcome 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.

Salmeterol xinafoate is a synthetic drug which is administered as an inhalation powder in the treatment of asthma. The drug substance will be manufactured at Glaxo Wellcome Operations in Montrose Scotland; micronized at Glaxo Wellcome Operations in Ware, England and at laboratoires Glaxo in Evreux, France; and formulated into final dosage form and packaged at Glaxo Wellcome Operations in Ware, England (page 001, attached). Lactose monohydrate is the only other component of the formulation. The finished drug product will be used in hospitals, clinics and by patients in their homes.

On page 006 (attached), the applicant indicates that the major route of drug substance emission into the environment is via urine and feces into waste water treatment systems. Based on its water solubility ($> 10^{-5}$ Molar) and octanol water partition coefficient of approximately 2, the applicant indicates that any drug substance not treated in waste water treatment plants will enter the aquatic environment. The acute toxicity to Daphnids is 48 hr EC50 = 20 mg/L and the NOEC = 6.7 mg/L.

Test results summarized in Appendix 4 (page 013 attached) indicate that salmeterol xinafoate readily degrades in the aquatic environment (biodegradation half life = 12.8 days in water (Attachment 4, data Summary Table, page 013, attached). The applicant refers to Serevent (salmeterol xinafoate) Inhalation Aerosol NDA-20236, Appendix E of the EA submitted May 11, 1992 for complete copies of the environmental fate and effects study reports for this drug substance.

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. Expired or returned drug product will be disposed of at the Glaxo Wellcome facility in Greenville, North Carolina in an incinerator operating between 1200F and 1850F (permit number 74-03-I, issued by the NC Division of Solid waste).

At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system while some unused drug may be disposed of in the sewer system.

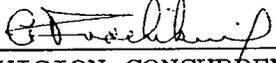
The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Glaxo Wellcome has received authorization from the appropriate authorities to operate the plant and has provided certification that operation is in accordance with applicable environmental regulations.

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.

5/21/97
DATE


PREPARED BY
Rik Lostritto, Ph.D.
Chemist
HFD-570

5/21/97
DATE


DIVISION CONCURRENCE
Guirag Poochikian
Chemistry Team Leader
HFD-570

6/9/97
DATE


CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

NEW DRUG APPLICATION

for

Serevent® (salmeterol xinafoate) Diskus® Inhalation Powder
NDA 20-692

VOLUME 6 - ENVIRONMENTAL ASSESSMENT

1. DATE	1
2. APPLICANT	1
3. ADDRESS	1
4. DESCRIPTION OF THE PROPOSED ACTION	1
4.a. Description of Requested Approval	1
4.b. Need for the Action	1
4.c. Locations where Products will be Produced	1
4.d. Sites of Product Use	3
4.e. Sites of Disposal	3
5. IDENTIFICATION OF CHEMICAL SUBSTANCES	4
5.a. Nomenclature	4
i. Established Name	4
ii. Proprietary Name	4
iii. Chemical Name	4
5.b. CAS Number - 94749-08-3	4
5.c. Molecular Formula - C ₂₅ H ₃₇ NO ₄ •C ₁₁ H ₈ O ₃	4
5.d. Molecular Weight	4
5.e. Structural Formula	4
5.f. Physical Description	4
5.g. Additives	5
5.h. Impurities	5
6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT	5
6.a. Substances Expected To Be Emitted	5
6.b. Controls Exercised	5
6.c. Citation And Statement Of Compliance With Applicable Emission Requirements	5
6.d. Effect Of Approval On Compliance With Current Emission Requirements	6
6.e. Expected Introduction Concentrations	6
6.e.i. Expected Introduction Concentrations From Use	6
6.e.ii. Introductions from Product Disposal	6
7.0 FATE OF SUBSTANCES IN THE ENVIRONMENT	6

ENVIRONMENTAL ASSESSMENT (cont'd)

8.0 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES	7
9.0. USE OF RESOURCES AND ENERGY	7
10.0. MITIGATION MEASURES	7
11.0. ALTERNATIVES TO THE PROPOSED ACTION	7
12.0. LIST OF PREPARERS	7
13.0. CERTIFICATION	8
14.0. REFERENCES	8
15.0. APPENDIXES	9
ATTACHMENTS	9
Attachment 1 Foreign Manufacturing Compliance Certification - Montrose.....	10
Attachment 2 Foreign Manufacturing Compliance Certification - Ware	11
Attachment 3 Foreign Manufacturing Compliance Certification - Evreux	12
Attachment 4 Data Summary Table.....	13
Attachment 5 Safety Data Sheet for Salmeterol Xinafoate.....	14
CONFIDENTIAL Attachment A EIC Calculations.....	21

Not attached

1. DATE

December 15, 1995

2. APPLICANT

Glaxo Wellcome Inc.

3. ADDRESS

Five Moore Drive
Research Triangle Park, NC 27709

4. DESCRIPTION OF THE PROPOSED ACTION

4.a. Description of Requested Approval

Glaxo Wellcome Inc. has filed an NDA pursuant to Section 505(b) of the Food, Drug and Cosmetic Act for Serevent[®] (salmeterol xinafoate) Diskus[™] Inhalation Powder. The device consists of a foil laminate strip containing either sixty pockets (60 dose) or twenty eight pockets (28 dose) each filled with 12.5mg of lactose and salmeterol xinafoate blend, and one empty pocket to test for any obstructions to the air flow. The strip is wound into a coil and inserted into a plastic device. The usual dosage is one blister (50 mcg per blister) twice daily.

4.b. Need for the Action

Salmeterol is a long-acting beta-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta2-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on .beta1- and .beta2-adrenoceptors. Serevent[®] Diskus[™] (salmeterol xinafoate) Inhalation Powder is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting .beta2-agonists. It should not be used in patients whose asthma can be managed by occasional use of short-acting, inhaled.beta2-agonists.

4.c. Locations where Products will be Produced

Salmeterol xinafoate will be manufactured in bulk form at Glaxo Wellcome Operations in Montrose, Scotland; micronised at Glaxo Wellcome Operations in Ware, England and at Laboratoires Glaxo in Evreux, France; and formulated into final dosage form and packaged at Glaxo Wellcome Operations in Ware, England.

Glaxo Wellcome Operations' Montrose facility is located in the town of Montrose, a small town in northeast Scotland between the cities of Aberdeen and Dundee. The town is mainly residential and commercial with a small amount of industry. Industries in the town include agriculture, fishing and oil field supply services in addition to pharmaceutical manufacturing. The facility itself is located adjacent to the North Sea at the mouth of the South Esk River. The site covers 45 acres and is approximately one mile due east of the Montrose Basin. The site is bounded to the east by the local beach and the North Sea, to the south by the estuary of the South Esk river and to the north by residential, commercial and industrial properties. The address of the Glaxo Wellcome Operations' Montrose facility is:

Glaxo Wellcome Operations
10 Cobden Street
Montrose
Angus DD10 8EB
Scotland, United Kingdom

Glaxo Wellcome Operations' Ware Facility is located in the town of Ware. Ware is a typical English market town some 20 miles from London having developed on the Lea Valley trackway from London. The town of Ware is located adjacent to Hertford, the county town of Hertfordshire, and is a short distance from the new towns of Harlow and Stevenage. Ware covers 2.2 square miles, has an approximate population of 17,600 and is within the region known as East Hertfordshire. The manufacturing facility itself is located on the River Lea. Land use immediately adjacent to the facility is residential to the north, recreational to the east and west, and to the south lies the River Lea Navigation. Land use throughout the district is predominantly agricultural with forestry and market gardening being of importance locally. Ware's industrial land is mainly confined to the central area of the town close to the river and railway. Industries in Ware include: malting; general engineering; steel founding; sand and gravel quarrying; coach building; electronics; pharmaceuticals manufacture and research; conveyor systems production; furniture manufacture; concrete production; plastics manufacture; building and construction; and graphic design. The address of the Glaxo Wellcome Operations' Ware facility is:

Glaxo Operations UK Ltd
Priory Street
Ware
Hertfordshire
SG12 0DJ
England

Evreux is the capital of Eure in northwest France. It is located approximately 100 kilometers from Paris. The town (population around 51,000) covers an area of approximately 2471 hectares. The Glaxo manufacturing facility is located in an industrial zone which covers an area of 84 hectares in a rural setting which is partially surrounded by the Evreux Forest. The facility is located on 15 hectares of which 4.6 hectares are covered by 15 buildings. The address of the Laboratoires Glaxo facility is:

Laboratoires Glaxo
23, Rue Lavoisier
Zone Industrielle No. 2
EVREUX CEDEX 9
27000 Evreux
France

4.d. Sites of Product Use

Serevent[®] Diskus[™] (salmeterol xinafoate) Inhalation Powder will be dispensed by prescription and used in private residences, hospitals, and clinics throughout the United States.

4.e. Sites of Disposal

Product that is introduced into the patient will be excreted in the urine and feces and distributed into wastewater treatment systems throughout the United States.

Returned and expired drug product is destroyed at the Glaxo Wellcome facility in Greenville, North Carolina. The facility is located northeast of the city of Greenville in Pitt County, North Carolina at the intersection of U.S. 13 North and State Road 1590. Pitt County is located in eastern North Carolina. The city of Greenville, with an estimated 1990 population of 48,000, is located in the center of the county approximately 50 kilometers southeast of Rocky Mount. Since the plant site is located in the coastal plain region of the state, terrain is extremely flat with terrain elevations changing only a few feet within a few kilometers of the plant site. The facility is located in an area zoned industrial. To the West-Northwest of the facility the land is zoned Residential/Agricultural. The returned drug is destroyed by a controlled air incinerator which operates at temperatures ranging of at least 1200°F in the primary chamber and 1850°F in the secondary chamber. The incinerator operates under permit number 74-03-I issued by the N.C. Division of Solid Waste. The permit expires July 7, 1997. The Address of the facility is:

Glaxo Wellcome Inc.
Corner of U.S. 13/NC11 and State Road 1590
Greenville, North Carolina 27834

5. IDENTIFICATION OF CHEMICAL SUBSTANCES

5.a Nomenclature

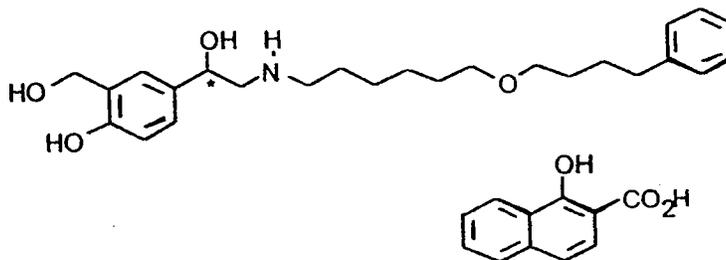
- i. **Established Name** - salmeterol xinafoate
- ii. **Proprietary Name** - Serevent®
- iii. **Chemical Name** - 4-Hydroxy- α -[[[6-(4-phenylbutoxy)hexyl]amino]-methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate

5.b **CAS Number** - 94749-08-3

5.c. **Molecular Formula** - $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$

5.d. **Molecular Weight** -603.8

5.e Structural Formula



*chiral centre

5.f. Physical Description

Salmeterol xinafoate is a white to off-white crystalline powder

5.g. Additives

Additives, including all excipient components and preservatives of the drug product, are listed below:

Chemical Name	CAS Number
Lactose	63-42-3

5.h. Impurities

Regulatory specifications for the drug substance limit total impurities to 1.2% with no single impurity being present at levels greater than 0.4%.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.a. Substances Expected To Be Emitted

As provided for in Section VI of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995), certifications are provided for Glaxo Wellcome's Montrose, Scotland and Ware, England facilities which manufacture the drug substance and drug product respectively. Attachment 1 contains the Montrose certification. Attachment 2 contains the certification for Ware. Attachment 3 contains the certification for Evreux.

6.b. Controls Exercised

As provided for in Section VI of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995), certifications are provided for Glaxo Wellcome's Montrose, Scotland and Ware, England facilities which manufacture the drug substance and drug product respectively. Attachment 1 contains the Montrose certification. Attachment 2 contains the certification for Ware. Attachment 3 contains the certification for Evreux.

6.c. Citation And Statement Of Compliance With Applicable Emission Requirements

As provided for in Section VI of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995), certifications are provided for Glaxo Wellcome's Montrose, Scotland and Ware, England facilities which manufacture the drug substance and drug product respectively. Attachment 1 contains the Montrose certification. Attachment 2 contains the certification for Ware. Attachment 3 contains the certification for Evreux.

6.d. Effect Of Approval On Compliance With Current Emission Requirements

As provided for in Section VI of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995), certifications are provided for Glaxo Wellcome's Montrose, Scotland and Ware, England facilities which manufacture the drug substance and drug product respectively. Attachment 1 contains the Montrose certification. Attachment 2 contains the certification for Ware. Attachment 3 contains the certification for Evreux.

6.e. Expected Introduction Concentrations

6.e.i. Expected Introduction Concentrations From Use

Administered drug product will enter the environment primarily through wastewater treatment facilities. The expected introduction concentration (EIC) for the aquatic environment of salmeterol from the use of Serevent[®] Diskus[™] (salmeterol xinafoate) Inhalation Powder and from the combined use of Serevent[®] Diskus[™] (salmeterol xinafoate) Inhalation Powder and Serevent[®] (salmeterol xinafoate) Inhalation Aerosol have both been calculated to be less than one part per billion (CONFIDENTIAL Attachment A).

6.e.ii. Introductions from Product Disposal

It is estimated that there will be no emissions to the environment from product disposal. All product in the United States that is returned is completely destroyed by high-temperature incineration at the facilities and under the permits discussed in Section 4.e.

7.0 FATE OF SUBSTANCES IN THE ENVIRONMENT

The major route of drug substance emission into the environment is via excretion in the urine and feces following product use and subsequent release into wastewater collection and treatment systems. Because the water solubility of the drug substance is greater than 10^{-5} molar and the octanol/water partition coefficient is approximately 2 (see Attachment 4) any drug substance not treated in the wastewater treatment plant should enter the aquatic environment. As discussed in Section 6.e.i the EIC for the aquatic compartment is expected to be less than 1 ppb. The expected environmental concentration (EEC) will be less than the EIC because the aerobic biodegradation rate of the drug substance ($T_{1/2}=12.8$ days see Attachment 4).

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

8.0 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

9.0. USE OF RESOURCES AND ENERGY

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

10.0. MITIGATION MEASURES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

11.0. ALTERNATIVES TO THE PROPOSED ACTION

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

12.0. LIST OF PREPARERS

This EA was prepared by:

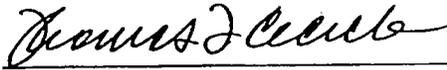
DOUGLAS S. FINAN

- Manager, Environmental Affairs, Glaxo Wellcome Inc.
1991 - present
- Environmental Safety Engineer, Glaxo Inc.
1990 - 1991
- Environmental Engineer, North Carolina Division of Environmental Management
1979-1990
- Environmental Specialist, Deltona Corporation
1978-79
- Bachelor of Science in Environmental Science & Engineering
Florida Institute of Technology, 1978

13.0. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of Glaxo Wellcome Inc.

The undersigned official certifies that the EA summary document pages 1-8 and Attachments 1-4 (pages 9 - 18) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR 1506.6.



Thomas F. Cecich

FEB 15, 1996

Date

Vice President, Safety & Environmental Affairs
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

14.0. REFERENCES

Center for Drug Evaluation and Research, "Guidance For Industry For the Submission Of An Environmental Assessment In Human Drug Applications And Supplements," Federal Register, November 1995

Council On Environmental Quality, " Regulations On Implementing National Environmental Policy Act Procedures," Federal Register, Vol. 43, November 29, 1978, p. 55990.

Glaxo Inc., "NDA 20-236; Serevent[®] (salmeterol xinafoate) Inhalation Aerosol, Environmental Assessment", May 1992

Pharmaceutical Manufacturers Association, "Interim Guidance To The Pharmaceutical Industry For Environmental Assessment Compliance Requirements For The FDA v7," Seminar on Environmental Assessments, Rockville, Md., July 29-30, 1991.

U.S. FDA, "Environmental Assessment Technical Assistance Handbook, U.S. FDA, March 1987

U.S. FDA, "National Environmental Policy Act; Policies and Procedures; Final Rule," Federal Register, Vol. 50, April 26, 1985

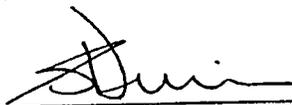
15.0. APPENDIXES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1ppb.

ATTACHMENTS

Attachment 1 Foreign Manufacturing Compliance Certification - Montrose

The Glaxo Wellcome manufacturing facility in Montrose, Scotland certifies that the facility is in compliance with or on an enforceable schedule to be in compliance with all local and national environmental laws and regulations including emission requirements set forth in permits, consent decrees and administrative orders, applicable to the production of Serevent® Diskus™ (salmeterol xinafoate) Inhalation Powder. Any increase in production at the facility needed to support the requested approval is not expected to affect compliance with current emission requirements or compliance with environmental laws and regulations.



Steve Davis

18/1/96.
Date

Safety, Health and Environmental Manager
10 Cobden Street
Montrose
Angus DD10 SE13
Scotland, United Kingdom

Attachment 2 Foreign Manufacturing Compliance Certification - Ware

The Glaxo Wellcome manufacturing facility in Ware, England certifies that the facility is in compliance with or on an enforceable schedule to be in compliance with all local and national environmental laws and regulations including emission requirements set forth in permits, consent decrees and administrative orders, applicable to the production of Serevent[®] Diskus[™] (salmeterol xinafoate) Inhalation Powder. Any increase in production at the facility needed to support the requested approval is not expected to affect compliance with current emission requirements or compliance with environmental laws and regulations.



Geoff Ogden

18th December 1995

Date

Safety, Health and Environmental Manager
Priory Street
Ware
Hertfordshire
SG12 0DJ
England

The Glaxo Wellcome manufacturing facility in Evreux, France certifies that the facility is in compliance with or on an enforceable schedule to be in compliance with all local and national environmental laws and regulations including emission requirements set forth in permits, consent decrees and administrative orders, applicable to the production of Serevent[®] Diskus[™] (salmeterol xinafoate) Inhalation Powder. Any increase in production at the facility needed to support the requested approval is not expected to affect compliance with current emission requirements or compliance with environmental laws and regulations.



Luc Parent4 Mar, 1996
Date

Safety, Health and Environmental Manager
Glaxo Wellcome Manufacturing
23, Rue Lavoisier
Zone Industrielle No. 2
EVREUX CEDEX 9
27000 Evreux
France

Attachment 4 Data Summary Table

Environmental Fate and Effects Study Results For Salmeterol Xinafoate¹

STUDY NAME	RESULTS			
Hydrolysis Rate	Hydrolytically stable over all pH ranges.			
Vapor Pressure	1.07 x 10 ⁻⁵ Torr at 24_C			
UV/Visible Spectra	Molar Extinction Coefficient (L/mol-cm)	Wavelength (nm)		
	4500	338		
	4350	327		
	3660	297		
Octanol/Water Partition Coefficient	Log10 Kow at			
	concentration (mole/L)	pH 5	pH 7	pH 9
	1 x 10 ⁻²	2.17	2.20	1.88
	1 x 10 ⁻³	2.06	1.87	1.55
	1 x 10 ⁻⁴		1.71	1.32
Dissociation Constant	pKa1 = 9.11 at 25_C pKa2 = 9.55 at 25_C			
Water Solubility at room temperature	pH 5	pH 7	pH 9	
	68.6 mg/l	67.0 mg/l	194 mg/l	
Soil Sorption/Desorption	Soil Type	K _d	K _{oc}	
	Kansas	141	6840	
	California	119	7480	
	Iowa	503	32900	
Biodegradation in Water	T _{1/2} = 12.8 days			
* ASRIT	EC ₅₀ = > 688 mg/l			
Acute Toxicity to Daphnids	48 hr EC ₅₀ = 20 mg/L NOEC = 6.7 mg/L			

¹ Complete copies of the environmental fate and effects study reports can be found in Appendix E of the EA submitted for Serevent® (salmeterol xinafoate) Inhalation Aerosol NDA 20-236, May 11, 1992.

Attachment 5 Safety Data Sheet for Salmeterol Xinafoate

ACCESSION NUMBER: 144

SHEET STATUS: Amended

FILE CODE: Authorised

CONFIDENTIALITY: Restricted

NAME: SALMETEROL XINAFOATE

SYNONYMS:

GR 33343G; salmeterol hydroxynaphthoate; Serevent;
4-hydroxy-alpha'-((((6-(4-phenylbutoxy)hexyl)amino)methyl)-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate.

MOLECULAR FORMULA: $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$

CAS REGISTRY NUMBER: 94749-08-3

RELATED REGISTRY NUMBER(S):

Not applicable

ITEM CODE: Not available

EINECS/ELINCS NUMBER: None assigned

SUBSTANCE IDENTIFICATION NO. (UN NO.): 8027

SUBSTANCE CLASS: Therapeutic agent; bronchodilator

DESCRIPTION

Salmeterol xinafoate is a white, crystalline solid very sparingly soluble in water.

MELTING POINT (deg.C): Approximately 138

BOILING POINT (deg.C): Not applicable

FLASH POINT (deg.C): Not applicable
440 (minimum ignition temperature)

AUTOIGNITION TEMPERATURE (deg.C): Not available

Safety Data Sheet for Salmeterol Xinafoate (continued)

UPPER EXPLOSIVE LIMIT (%): Not available

LOWER EXPLOSIVE LIMIT (%): See 'Fire'.

CONDUCTIVITY (pS/m): 10 - 100 (micronised powder)

RESISTIVITY (ohm.cm): $10(\text{exp}12)$ - $10(\text{exp}13)$ (micronised powder)

VAPOUR DENSITY (air=1.0): Not applicable

SPECIFIC GRAVITY/DENSITY: Approximately 0.25 g/ cm³ (bulk density)

WATER SOLUBILITY/MISCIBILITY (%w/v): 0.009 at 20 deg.C (Insoluble); 0.67 at pH 7

PARTITION COEFFICIENT: 1.56

GAS GROUP: 1.93

CHEMICAL AND THERMAL

Salmeterol xinafoate is relatively stable. Differential scanning calorimetry shows no evidence of thermal decomposition up to 140 deg.C

FIRE

Salmeterol xinafoate is not readily ignited, but on strong heating flammable, toxic vapours including oxides of nitrogen, may be evolved.

The following properties have been determined for micronised salmeterol xinafoate:

Minimum explosible concentration 10 g/m³

Minimum ignition energy 5-8 mJ

Minimum ignition temperature (as dispersed dust) 440 deg.C

Minimum ignition temp. (as powder layer) - no exothermic reaction up to melting point

Powder resistivity $10(\text{exp}14)$ - $10(\text{exp}15)$ ohm.m

Minimum oxygen concentration (for combustion) 9.8% by volume

Chargeability tests indicate that salmeterol xinafoate can present a moderate to high static electrical discharge hazard if poured.

Safety Data Sheet for Salmeterol Xinafoate (continued)

CORROSION

No information is available.

BIOLOGICAL EFFECTS

Salmeterol xinafoate is the hydroxynaphthoate salt of the pharmacologically active base salmeterol. It is a potent and long-lasting pharmacological agent with proven efficacy in the treatment of asthma by inhalation. It is believed to act by both relaxing smooth muscle and inhibiting inflammation in the airways.

Salmeterol xinafoate can be moderately irritant to abraded skin under occlusion and is a severe eye irritant.

It is non-irritant to intact skin and there is no evidence that it is a skin sensitiser.

Salmeterol xinafoate is pharmacologically active by the inhaled route. Inhalation of very high doses can cause localised irritant changes in the larynx of the rat, but extensive clinical studies have confirmed that these are not relevant at therapeutic doses.

Repeat dosing of animals with excessive doses produced the predictable effects known to be associated with this class of compound, including transient vasodilatation and reflex increases in heart rate as immediate responses to dosing, and increased body weight gain and repartitioning of fat and muscle at very high dosages. Animals tolerated the excess doses well for periods of 12 to 18 months. There is no evidence that these effects have any relevance to humans receiving therapeutic doses.

Information from large numbers of patients and volunteers indicate that salmeterol xinafoate is well tolerated. The following symptoms occurred in volunteers after inhaled doses of 100 micrograms or more: increased heart rate, tremor, headache, increased blood glucose and decreased blood potassium.

In common with other drugs of this class, administration of salmeterol xinafoate to pregnant animals caused abnormalities of foetal development. Extensive clinical use of these agents over many years, including their deliberate use in pregnancy, suggests that the effects do not occur in man.

Salmeterol xinafoate has been shown to have no activity in animal and laboratory tests for mutagenicity.

Rodents exposed to excess doses of salmeterol xinafoate in lifetime studies developed a low incidence of benign smooth muscle tumours. There is good evidence that these effects are species specific and of no relevance for humans.

Safety Data Sheet for Salmeterol Xinafoate (continued)

Solid Spillage

Collect the spillage by vacuum and transfer to a suitably labelled, sealable, container e.g. a double polythene bag. Wash the contaminated area with running water and detergent to an effluent drain to remove the last traces of spill.

Liquid Spillage

Remove all possible sources of ignition. Contain the spillage by improvising dams with sand or other inert material. If possible, transfer the liquid to a sealable, labelled container for re-use or recovery. Otherwise, absorb on sand or other inert material and remove for disposal in a safe place. Wash the contaminated area with copious quantities of water and detergent to an effluent drain to remove the last traces of spill.

Test the area and assess the risk of exposure before allowing unprotected re-entry and the resumption of normal working practices.

UK CLASSIFICATION, PACKAGING AND LABELLING:

Salmeterol xinafoate is not listed under the Chemicals (Hazard Information and Packaging) Regulations, 1993. However, suitable labelling for bulk quantities would be:

Hazard Symbol

Irritant

Risk Phrases

R36: Irritating to eyes.

Safety Phrases

S36/ 37/ 39: Wear suitable protective clothing, gloves and eye protection.

INTERNATIONAL TRANSPORT CLASSIFICATION:

AIR

Passenger Instruction 906

Cargo Instruction 906

UN Class 9

Proper Shipping Name OTHER REGULATED SUBSTANCES

Hazard Miscellaneous

AUTHORISING PERSON(S): Dr SJ Burge, Glaxochem Ltd.

DATE: Jan 20, 1994

Safety Data Sheet for Salmeterol Xinafoate (continued)

The oral LD50 of salmeterol xinafoate is in excess of 1g per kg.

Toxicity rating: Not applicable (It is a severe eye irritant.)

ENVIRONMENTAL EFFECTS

Salmeterol xinafoate is readily biodegradable in water achieving 50% degradation in 12.8 days. The dissociation constant is pKa1 is 9.11 and pKa2 is 9.55. The vapour pressure is 1.07×10^{-5} . Salmeterol xinafoate is hydrolytically stable over all pH ranges tested.

The soil absorption/desorption test results are as follows:

Kansas Kd 141, Koc 6,840

California Kd 119, Koc 7,480

Iowa Kd 503, Koc 32,900

There is a low risk of toxicity to Activated Sludge, the ASRIT EC50 is greater than 688 mg/l (as the active substance).

Salmeterol xinafoate is harmful to daphnia with a 48 hour EC50 of 20 mg/l (active ingredient) and a No Observed Effect Level of 6.7 mg (active ingredient)/l.

Emissions and discharges must be kept to a minimum and comply with any requirements laid down by regulatory bodies.

OCCUPATIONAL EXPOSURE

Occupational Exposure Level (Glaxo) TWA (8 hr) 0.001 mg/m³ (Provisional)

OCCUPATIONAL HYGIENE MONITORING

Reference should be made should be made to the Group Occupational Health and Hygiene Manual.

Airborne concentrations may be determined by collecting samples on a suitable filter with subsequent analysis by HPLC. A validated method is available.

Safety Data Sheet for Salmeterol Xinafoate (continued)

HEALTH SURVEILLANCE

Any symptoms apparently due to exposure to salmeterol hydroxynaphthoate must be reported to the Occupational Health Department/Occupational Health Physician and Line Management without delay.

Health surveillance should be appropriate to the risk and must be determined only after a risk assessment has been carried out.

PERSONAL PROTECTIVE EQUIPMENT

The selection of protective equipment should be based on an assessment of potential levels of exposure. Reference should be made to the Group Occupational Health and Hygiene Manual.

An air suit, impervious gloves and boots may be required when salmeterol xinafoate is handled outside an enclosed system. Any respiratory protection should also provide skin and eye protection. If there is significant risk of contamination of eyes, skin or clothing, the provision of suitable goggles, impervious gloves and disposable overalls must be considered.

HANDLING AND STORAGE

Store below 30 deg.C in a dry place in sealed containers (e.g. double polythene bags inside closed and labelled kegs). Cleansing of containers should be performed by using special methods as salmeterol xinafoate is not soluble in water.

Wherever possible, salmeterol xinafoate should be handled in enclosed plant fitted with exhaust ventilation.

DISPOSAL

Consideration must be given to recovery operations. However, if disposal is necessary, this may best be effected by dissolving in a suitable flammable solvent and burning the solution in a licensed incinerator.

Disposals must conform to relevant legislation.

FIRST AID

A severe eye irritant. Pharmacologically active by inhalation, it can cause transient vasodilatation following high clinical dosage. Tremor and headache are known side effects.

Safety Data Sheet for Salmeterol Xinafoate (continued)

NEVER attempt to give any solid or liquid by mouth to an unconscious person.

Eyes

Wash immediately with plenty of water from any eye wash fountain or bottles and continue for at least 15 minutes. Obtain medical attention promptly.

Skin Contact

Thoroughly wash all affected areas with soap and water, removing contaminated clothing. Obtain medical attention. Thoroughly wash contaminated clothing.

Inhalation

Remove the casualty to fresh air, and if breathing is difficult or ceases, give oxygen or mouth to mouth resuscitation. The casualty should be kept warm and at rest. Obtain medical attention.

Ingestion

Wash out the mouth and give water to drink. Obtain medical attention.

EMERGENCY MEDICAL TREATMENT

The preferred antidote following overdose is a cardio-selective, beta-blocking agent, but beta-blocking drugs should be used with caution in patients with a history of bronchospasm.

EMERGENCY ACTION CODE (HAZCHEM CODE): 2X

FIRE FIGHTING

Wear breathing apparatus and clothing designed to give full skin and eye protection.

Use water fog or spray, dry powder or foam.

LEAKAGE/SPILLAGE

Wear an air suit, gloves and boots or respiratory protection such as breathing apparatus and clothing designed to give full skin and eye protection. Unprotected personnel should not be permitted to enter the spillage area. If possible stop the spillage. Avoid raising dust. Isolate the hazardous area.