CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20692

CHEMISTRY REVIEW(S)

FEB 5 1997

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

NDA #:	20-692	CHEM. REVIEW #	1	REVIEW DATE:	02/04/97
SUBMISSION TYPE		DOCUMENT DATE	CDER DATE	ASSIGNED DATE	
ORIGINAL*		6/18/96	6/19/94	7/01/96	

* subject of this review

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

DRUG PRODUCT NAME

Proprietary:	Serevent (salmeterol xinafoate)Diskus Inhalation Powder
Nonproprietary/USAN:	salmeterol xinafoate inhalation powder
Code Name/#:	none
Chem.Type/Ther.Class:	bronchodilator

PHARMACOL. CATEGORY/INDICATION: long acting bronchodilator (beta$_2$-adrenoceptor agonist) for relief of bronchospasm.

DOSAGE FORM: Metered Dose Powder for Inhalation (MDPI)
STRENGTHS: 72.5 mcg salmeterol xinafoate ***equivalent to*** 50.0 mcg salmeterol base per metered dose

28 and 60 metered dose drug products.

ROUTE OF ADMINISTRATION: Oral Inhalation
DISPENSED: _X_ Rx ___ OTC

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

See USP Dictionary of USAN and International Drug Names, 1996, page 624.

SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DMFs and Other Supporting Documents

Document No.	Holder Name	Subject	Status	Date Reviewed 1*	Reference in CR#1
NDA 20236	Glaxo Wellcome	Serevent (salmeterol xinafoate) Inhalation Aerosol	approved	not applicable	not applicable

*1 Letter date if deficient.

RELATED DOCUMENTS (if applicable):

NDA 20236 for Serevent Inhalation Aerosol. This is the currently marketed metered dose inhaler dosage form of salmeterol xinafoate.

CONSULTS:

Statistics: For stability data analysis Status: To be initiated after the applicant responds to comments from this review regarding stability.

Microbiology: May be initiated based on the applicant's response to comments from this review regarding microbial controls of drug substance, excipients and drug product.

Nomenclature: (not needed)

Environmental Assessment (EA): To be initiated

Establishment Evaluation Request (EER): Initiated 09/23/96, Status: Pending

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

There are deficiencies in the drug substance, excipient, drug product, container closure, specifications and controls and stability sections of this NDA. The applicant should be informed of these deficiencies in a letter. **If all deficiencies are not satisfactorily resolved, this NDA should be "not approvable".**

cc:
Org. NDA 20-503
HFD-570/Division File
HFD-570/PJani (CSO)
HFD-570/R.Lostritto
HFD-570/GPoochikian

02/04/97
Richard Lostritto, Ph.D. Review Chemist

2/5/97
Guirag Poochikian, Ph.D. Supervisory Chemist

R/D Init by: _____

filename: N:\nda\20692\chem\97-02-04.rev

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

NDA #: 20-692 **CHEM. REVIEW #** 2 **REVIEW DATE:** 06/11/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	6/18/96	6/19/96	7/01/96
AMENDMENT [BC]*	4/17/97	4/19/87	4/23/97

* subject of this review

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

DRUG PRODUCT NAME

Proprietary:	Serevent (salmeterol xinafoate)Diskus Inhalation Powder
Nonproprietary/USAN:	salmeterol xinafoate inhalation powder
Code Name/#:	none
Chem.Type/Ther.Class:	bronchodilator

PHARMACOL. CATEGORY/INDICATION: long acting bronchodilator (beta$_2$-adrenoceptor agonist) for relief of bronchospasm.

DOSAGE FORM: Metered Dose Powder for Inhalation (MDPI)
STRENGTHS: 72.5 mcg salmeterol xinafoate ***equivalent to*** 50.0 mcg salmeterol base per metered dose

28 and 60 metered dose drug products.

ROUTE OF ADMINISTRATION: Oral Inhalation
DISPENSED: _X_ Rx ___ OTC

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

See USP Dictionary of USAN and International Drug Names, 1996, page 624.

SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DMFs and Other Supporting Documents

Document No.	Holder Name	Subject	Status	Date Reviewed 1*	Reference in CR#1
NDA 20236	Glaxo Wellcome	Serevent (salmeterol xinafoate) Inhalation Aerosol	approved	not applicable	not applicable

*1 Letter date if deficient.

RELATED DOCUMENTS (if applicable):

NDA 20236 for Serevent Inhalation Aerosol. This is the currently marketed metered dose inhaler dosage form of salmeterol xinafoate.

CONSULTS:

Statistics: For stability data analysis Status: To be initiated after the specifications have been set for the critical attributes.

Microbiology: May be initiated based on the applicant's response to comments from this review regarding microbial controls of drug product

Nomenclature: (not needed)

Environmental Assessment (EA): EA review forwarded to the Center EA Officer and it has been signed off by that Officer.

Methods Validation: Will be initiated when all methods and specifications are found satisfactory.

Establishment Evaluation Request (EER): Initiated 09/23/96, Status: Pending

REMARKS/COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

CONCLUSIONS & RECOMMENDATIONS:

There are deficiencies in the micronized drug substance, excipient, drug product, container closure, specifications and controls and stability sections of this NDA. The applicant should be informed of these deficiencies in a letter.

06/18/97
Richard Lostritto, Ph.D. Review Chemist

Guirag Poochikian, Ph.D. Chemistry Team Leader

R/D Init by: 6/19/97

filename: N:\nda\20692\chem\97-06-19.rev

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

NDA #: 20-692 **CHEM. REVIEW #** 3 **REVIEW DATE:** 8/14/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	6/18/96	6/19/96	7/01/96
AMENDMENT [BC]	4/17/97	4/17/97	4/17/97
AMENDMENT [AC]*	5/30/97	6/92/97	6/02/97
AMENDMENT [BC]*	6/18/97	6/19/97	6/25/97
AMENDMENT [BC]*	7/22/97		

* subject of this review

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

DRUG PRODUCT NAME

Proprietary:	Serevent (salmeterol xinafoate)Diskus Inhalation Powder
Nonproprietary/USAN:	salmeterol xinafoate inhalation powder
Code Name/#:	none
Chem.Type/Ther.Class:	bronchodilator

PHARMACOL. CATEGORY/INDICATION: long acting bronchodilator (beta$_2$-adrenoceptor agonist) for relief of bronchospasm.

DOSAGE FORM: Metered Dose Powder for Inhalation (MDPI)
STRENGTHS: 72.5 mcg salmeterol xinafoate ***equivalent to***
50.0 mcg salmeterol base per metered dose

28 and 60 metered dose drug products.

ROUTE OF ADMINISTRATION: Oral Inhalation
DISPENSED: _X_ Rx ___ OTC

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

See USP Dictionary of USAN and International Drug Names, 1996, page 624.

SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DMFs and Other Supporting Documents

Document No.	Holder Name	Subject	Status	Date Reviewed 1*	Reference in CR#1
NDA 20236	Glaxo Wellcome	Serevent (salmeterol xinafoate) Inhalation Aerosol	approved	not applicable	not applicable

*1 Letter date if deficient.

RELATED DOCUMENTS (if applicable):

NDA 20236 for Serevent Inhalation Aerosol. This is the currently marketed metered dose inhaler dosage form of salmeterol xinafoate.
NDA 20692 Chemistry Amendment dated 4/17/97 (see CR #2).

CONSULTS:

Statistics: For stability data analysis Status: Will be initiated using Agency "e.g." values for PSD specifications.

Nomenclature: (not needed)

Environmental Assessment (EA): EA review forwarded to the Center EA Officer and it has been signed off by that Officer.

Methods Validation: Will be initiated when all methods and specifications are found satisfactory.

Establishment Evaluation Request (EER): Initiated 09/23/96, Status: Pending
Updated 4/17/97, Status: Pending

REMARKS/COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

There are deficiencies in the excipient, drug product, container closure, specifications and controls and stability sections of this NDA. The applicant should be informed of these deficiencies in a letter.

8/14/97
Richard Lostritto, Ph.D. Review Chemist

8/14/97
Guirag Poochikian, Ph.D. Chemistry Team Leader

R/D Init by: _____

filename: N:\nda\20692\chem\97-05-30.rev

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ON ORIGINAL

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APPEARS THIS WAY
ON ORIGINAL

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

NDA #: 20-692 **CHEM. REVIEW #** 4 **REVIEW DATE:** 9/18/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	6/18/96	6/19/96	7/01/96
AMENDMENT [BC]	4/17/97	4/17/97	4/17/97
AMENDMENT [AC]	5/30/97	6/92/97	6/02/97
AMENDMENT [BC]	6/18/97	6/19/97	6/25/97
AMENDMENT [BC]	7/22/97		
AMENDMENT [BZ]*	8/22/97	8/25/97	8/25/97
AMENDMENT [BC]*	8/24/97		8/25/97
AMENDMENT [BC]*	9/12/97		
AMENDMENT [BC]*	9/15/97		
AMENDMENT [BC]*	9/15/97		

*** subject of this review**

NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

DRUG PRODUCT NAME

Proprietary:	Serevent (salmeterol xinafoate)Diskus Inhalation Powder
Nonproprietary/USAN:	salmeterol xinafoate inhalation powder
Code Name/#:	none
Chem.Type/Ther.Class:	bronchodilator

PHARMACOL. CATEGORY/INDICATION: long acting bronchodilator (beta$_2$-adrenoceptor agonist) for relief of bronchospasm.

DOSAGE FORM: Metered Dose Powder for Inhalation (MDPI)
STRENGTHS: 72.5 mcg salmeterol xinafoate ***equivalent to***
50.0 mcg salmeterol base per metered dose

28 and 60 metered dose drug products.

ROUTE OF ADMINISTRATION: Oral Inhalation
DISPENSED: _X_ Rx ___ OTC

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

See USP Dictionary of USAN and International Drug Names, 1996, page 624.

SUPPORTING DOCUMENTS:

APPEARS THIS WAY
ON ORIGINAL

DMFs and Other Supporting Documents

Document No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1

NDA 20236	Glaxo Wellcome	Serevent (salmeterol xinafoate) Inhalation Aerosol	approved	not applicable	not applicable

RELATED DOCUMENTS (if applicable):

NDA 20236 for Serevent Inhalation Aerosol. This is the currently marketed metered dose inhaler dosage form of salmeterol xinafoate.
NDA 20692 Chemistry Review # 3 dated 8/14/97

CONSULTS:

Statistics: For stability data analysis: Initiated 8/22/97. Status: Pending. NOTE: [BZ} amendment dated 8/22/97 has been forwarded to the Statistician (Gebert) as part of this consult. This consult has been completed and is discussed herein. [The stability results analysis by the statistician does not support a 24 month shelf life.]

Nomenclature: (not needed)

Environmental Assessment (EA): EA review forwarded to the Center EA Officer and it has been signed off by that Officer.

Methods Validation: Will be initiated when all methods and specifications are found satisfactory. NOTE: Volume 2 of the 8/24/97 [BC] amendment contains an updated and now outdated methods validation package. THE APPLICANT WILL BE ASKED TO PROVIDE AN UPDATED METHODS VALIDATION PACKAGE.

Establishment Evaluation Request (EER): Initiated 09/23/96,
Amended 4/15/97. Status: Pending

REMARKS/COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

There are several CMC issues remaining regarding the control of the quality of the drug product. Most notable of these, the applicant agrees to evaluate in greater detail, their proposed 8 week patient-use-life for the unwrapped drug product. The applicant agrees to an interim report date of 12/31/97 (or 90 days from start of stability studies) to substantiate the patient-use-life.

The **Project Manager** will follow up on the pending EER results and will forward the updated Methods Validation Package. The updated Methods Validation package is expected prior to product launch and will reflect all changes noted

Based on this and the other commitments noted ....., this application may be approved from a CMC view point. It is recommended that this NDA (20-692) be approved.

9/18/97
Richard Lostritto, Ph.D. Review Chemist

Guirag Poochikian, Ph.D. Chemistry Team Leader

R/D Init by: 9/18/97

filename: N:\nda\20692\chem\97-09-19.rev

APPEARS THIS WAY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20692

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

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.

APPEARS THIS WAY
ON ORIGINAL

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)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

NEW DRUG APPLICATION

for

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

VOLUME 6 - ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT (cont'd)

Not attached

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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®

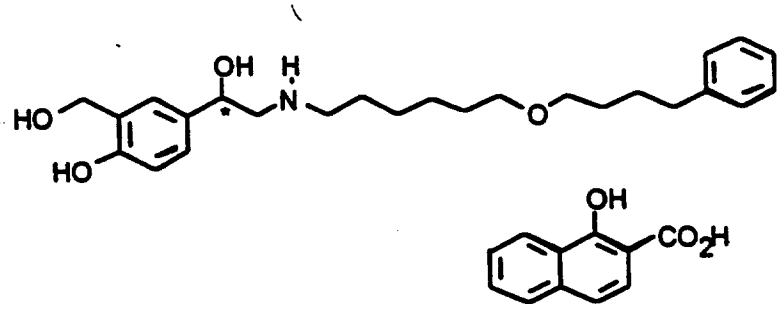
iii. **Chemical Name** - 4-Hydroxy-a^1-[[[6-(4-phenylbutoxy)hexyl]amino]-methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate

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.

C Ogden

Geoff Ogden

18th December 1995

Date

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

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Attachment 3 **Foreign Manufacturing Compliance Certification - Evreux**

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 Parent

4 Mars 1996
Date

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

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Attachment 4 **Data Summary Table**

Environmental Fate and Effects Study Results For Salmeterol Xinafoate[1]

STUDY TYPE	RESULTS
Hydrolysis Rate	Hydrolytically stable over all pH ranges.
Vapor Pressure	1.07×10^{-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
1×10^{-2}	2.17	2.20	1.88
1×10^{-3}	2.06	1.87	1.55
1×10^{-4}		1.71	1.32

Dissociation Constant

$pK_{a1} = 9.11$ at 25_ C

$pK_{a2} = 9.55$ 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.

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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: $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$

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

UPPER EXPLOSIVE LIMIT (%): Not available

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

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

RESISTIVITY (ohm.cm): 10(exp12) - 10(exp13) (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(exp14) - 10(exp15) 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.

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 believe 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 show 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.

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

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 x 10(exp 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.

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.

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 overdosage 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20692

PHARMACOLOGY REVIEW(S)

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF TOXICOLOGY DATA
ORIGINAL REVIEW No. 1

NDA 20-692

Information to be Conveyed to Sponsor: Yes (X), No ( )

Date of Submission: 6/18/96
10/8/96

Reviewer: Lawrence F. Sancilio, Ph.D.

Date Completed: 5/13/97

Sponsor: Glaxo Inc.
5 Moore Drive
Research Triangle Park, NC 27709

Drug Names: Salmeterol xinafoate(GR 33343G)
GR97980X

Chemical Name: Salmeterol xinafoate (4-Hydroxy-α^1-[[6-(4-phenylbutoxy)hexyl) amino]-methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate)

GR97980X: 1-Hydroxy-4-[{2-hydroxy-5-{1-hydroxy-2-{{6-(4-phenylbutoxy)-hexyl}amino}ethyl}phenyl}methyl}]2-naphthalenecarboxylic acid

Structure:

Class: Salmeterol xinafoate, B_2 Adrenoceptor Agonist
GR97980X, Degradant

Indication: Treatment of reversible bronchoconstrictive airway disorders

Related NDA: NDA 20-236, salmeterol metered dose inhaler
IND
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Description of Product: The Diskus Inhalation powder is a dry powder formulation containing micronized salmeterol xinafoate and lactose monohydrate NF. The Diskus is a 60 unit-dose pack in a self-contained device with a dose counter. Each dose consists of 50 μg of salmeterol xinafoate and 12.5 mg of lactose in a double foil blister consisting of aluminum foil laminate. Lactose was chosen as the diluent since it has been used extensively in other powdered formulations and forms a free-flowing blend with salmeterol xinafoate. The clinical inhalation dose for salmeterol xinafoate is 50 μg twice a day.

Background for Submission of Preclinical Studies

It was found that when formulating the salmeterol xinafoate- lactose powder mix, a degradant, GR97980X, was formed; this was caused by the condensation of salmeterol with hydroxynaphthoic acid. Since the proposed upper limit concentration of GR97980X in the salmeterol was 3% which exceeded the upper acceptable level of 1%, safety studies were necessary. This NDA submission includes pharmacologic and toxicologic studies conducted with the degradant, GR97980X.

STUDIES SUBMITTED

PHARMACOLOGY

Pharmacologic studies with GR97980X, No. NPY/95/010, vol. 7, p 28.

PHARMACOKINETICS/METABOLISM

Aliphatic oxidation of salmeterol to α hydroxysalmeterol in human liver microsomes by cytochrome P-4503A4, No. WBP/93/062, vol. 10, p 268.

Major metabolite of salmeterol in the beagle dog after p.o. administration of 0.25 mg/kg of salmeterol xinafoate, No. WBP/95/006, vol. 10, p 289.

TOXICOLOGY

Single Dose

Preliminary Acute toxicity of GR97980X p.o. in rats, NPY/91/010, vol. 7, p 75.
Acute toxicity of GR97980X p.o. in rats, NPY/91/011, vol. 7, p 75.
Acute toxicity of inhaled GR97980X in rats, WPT/91/337, vol. 7, p 131.

Multidose

Salmeterol xinafoate: aged lactose powder mixture: 13 Weeks inhalation toxicity study in rats, WPT/89/219, vol. 7, p 337.

Salmeterol xinafoate and GR97980X (powder formulation): 13 Weeks inhalation toxicity study in dogs, No. D21268, vol. 5.1, p 1.

Genotoxicity

Microbial mutagenicity assay on salmeterol xinafoate aged lactose No. WPT/90/12, vol. 10, p 105.

REVIEW

Studies Not Reviewed: None.

PHARMACOLOGY

Pharmacologic studies with GR97980X, No. NPY/95/010, vol. 7, p 28.

In the isolated guinea pig tracheal preparation, GR97980X at concentrations from 10^{-10}M-10^{-6}M did not affect the contraction induced by histamine. At the same concentrations salmeterol xinafoate did not increase the spontaneous beating rate of the guinea pig right isolated atria. In both studies isoproterenol, a reference β_1 or β_2 agonist, at 10^{-6}M produced significant relaxation of the histamine-induced contraction of the trachea and a significant increase the spontaneous beating rate of the guinea pig right isolated atria.

Conclusion

In the guinea pig tracheal and atrial preparations, GR97980X is not a β_1 or β_2 agonist.

PHARMACOKINETICS/METABOLISM

Aliphatic oxidation of salmeterol to α hydroxysalmeterol in human liver microsomes by cytochrome P-4503A4, No. WBP/93/062, vol. 10, p 268.

Method

Radiolabeled C^{14} salmeterol, 10μM, was incubated in human liver microsomes in the presence of selective inhibitors of the P450 enzyme systems. They are listed in the following table along with their selectivity and concentrations tested. Analyses for metabolites were determined by thin layer chromatography and gas chromatography-mass spectrometry.

Inhibitor/ Concentration, μM	Isoenzyme Inhibited
Ketoconazole, 1	CYP3A4
Furafylline, 10 or 100	CYP1A2
Quinidine, 10	CYP2D6
Sulfaphenazole, 10	CYP2C9
Disulfuram, 10	CYP2E1

Results

Conversion of salmeterol to α hydroxysalmeterol was completely inhibited by ketoconazole and partially by disulfuram indicating that the P450 enzymes CYP3A4 and CYP2E1 are involved in the metabolism of salmeterol.

Conclusion

P450-CYP3A4 and -CYP2E1 are involved in the metabolism of salmeterol in humans.

Major metabolite of salmeterol in the beagle dog after p.o. administration of 0.25 mg/kg of salmeterol xinafoate, No. WBP/95/006, vol. 10, p 289.

Method

Two and one-half mg/kg p.o. of radiolabeled C^{14} salmeterol xinafoate were administered to 2 M beagle dogs with cannulated bile ducts. Following administration, blood was removed at 0.75, 1, 1.5 and 2 h, bile was collected up to 8 h, 23-24 and 47-48 h and urine and feces were collected up to 48 h. Only the bile and urine were analyzed for salmeterol xinafoate and major metabolite(s). The major metabolite(s) were determined by HPLC analyses, Mass Spectrometry and NMR. A combination of LCMSMS was used to identify the structure of the metabolite(s).

Results

Seventeen percent and 13% of the salmeterol xinafoate dose was recovered in the bile and urine, respectively. In the bile only one major metabolite was found; it was identified as the 3-catechol sulfate of the benzoic acid derivative; its structure is presented below. Three minor metabolites found in the bile were identified by chromatographic analysis; their structures were not identified. No urinary data was presented. The sponsor indicated that the aim of the study was to identify the major metabolite in the bile which was previously shown in bile duct cannulated animals.

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Conclusion

In the dog, the principal metabolite of salmeterol found in the bile was identified as the 3-catechol sulfate of the benzoic acid derivative.

TOXICOLOGY

Single Dose

Preliminary Acute toxicity of GR97980X p.o. in rats, NPY/91/010, vol. 7, p 75.
Acute toxicity of GR97980X p.o. in rats, NPY/91/011, vol. 7, p 75.
Acute toxicity of inhaled GR97980X in rats, WPT/91/337, vol. 7, p 131.

The results summarized in the following table show that GR97980X in rats was not toxic at 768 (GLP study) mg/kg p.o. By the inhaled route GR97980X produced decreased body weight gained in F at approximately 60 mg/kg; No toxicity was seen at approximately 37 mg/kg.

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Rat Strain/No./Group Duration Dose, mg/kg	Route	Observations
CD (Crj:CD), 2 M +2 F/Group, 98-122 g, B.W. 6 Days Observation		Preliminary Study
435	p.o.	No deaths, no clinical signs and no macropathology
870		No deaths, no clinical signs and no macropathology
CD (Crj:CD), 5 M +5 F/Group, C, HD 97-125 g, B.W. 14 Days Observation	p.o.	GLP Statement
768		No deaths, no clinical signs and no macropathology
AHA, 5 M +5 F/Group, 129-172 g, B.W. C, Lactose, LD, HD 14 Days Observation	Inhalation Snout only, 1 h Exposure	GLP Statement
LD, ca 37 MMAD, 1.78 μm		No deaths, no clinical signs and no macropathology
HD, ca 60 MMAD, 1.46 μm		M, No deaths, no clinical signs and no macropathology F, -29% ↓ body weight gained, 0-14 days; otherwise, no deaths, no clinical signs and no macropathology.

Conclusion

In single dose studies in rats, the NOAEL was 768 mg/kg p.o. and approximately 37 mg/kg by the inhaled route. No target organs were identified.

Multidose

Salmeterol xinafoate: aged lactose powder mixture: 13 Weeks inhalation toxicity study in rats, WPT/89/219, vol. 7, p 337.

There was a signed GLP statement.

Study Site:

Study Dates: 4/10/89- 7/17/89

Method

Animals: Crl:CD (SD) BR strain 20 M (mean body weight, 158 g) and 20 F (mean body weight, 114 g). Of these 20 animals eight M and F in each group were used in the pharmacokinetics analyses.

Compounds: Salmeterol xinafoate with degradant, GR97980X.
Batch No. U89/309A and U89/307A of salmeterol xinafoate in lactose contains 0.2% w/w of the degradant, GR97980X.
Batch No. U89/306 of salmeterol xinafoate in lactose contains 1.8% w/w of the degradant, GR97980X.

Route: Inhalation.

Doses: The following daily doses were administered daily over 1 h by inhalation (snout only) for 13 weeks, Control, lactose only (C), 0.07 mg/kg of salmeterol base + 0.0029 mg/kg of GR97980X (LD) and 0.64 mg/kg of salmeterol base + 0.0033 mg/kg of GR97980X (HD). These preparations were artificially aged by storage at 65°C for 30 days to produce the degradant, GR97980X.

The following parameters were determined.

Particle Size of Aerosol: Mass median aerodynamic diameter (MMAD) and geometric standard deviation were determined during weeks 1, 3, 7, and 13.

Clinical Observations: Daily.

Body Weight: Prior to initiation of study and thereafter, weekly.

Food Consumption: Prior to initiation of study and thereafter, weekly; results were expressed as g/rat/week.

Ophthalmic Examination: Prior to initiation of study and on week 13.

Hematology Clinical Chemistry and Urinalysis, weeks 5 and 13 of study.

Plasma Levels: At the end of dosing on day 1 and during weeks 4 and 13.

Necropsy

All animals were examined macroscopically. The following organs were weighed: adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, spleen, gonads, thymus and uterus.

Histopathology: The following tissues were examined by light microscope:
adrenals, alimentary tract, oesophagus, stomach, duodenum, jejunum, ileum, caecum colon, rectum, aorta, brain, eyes, Harderian gland, lachrymal gland, eyelids, optic nerve femur (with joint), kidneys, larynx, liver, lungs, lymph nodes (tracheobronchial, cervical, mesenteric), mammary gland, muscle (thigh), nasal passages (head[a] for rostral and caudal nasal cavities), ovaries, pancreas, pharynx, pituitary, prostate, salivary gland, sciatic nerve, seminal vesicles, spinal column, spinal cord, (cervical), spleen, sternum (for bone and marrow), testes (with epididymides), thymus, thyroid (with parathyroids), tongue (nerve muscle), trachea (including bifurcation), urinary bladder, uterus (corpus and cervix) and vagina.

[a] The remaining head was retained for paranasal sinuses, oral cavity, nasopharynx, middle ear, teeth and Zymbal.

All tissues in C and HD groups were examined. Tissues examined in the LD group were: lungs larynx, nasal passages (head[a] for rostral and caudal nasal cavities) and trachea (including bifurcation and uterus.

Results

Particle Size of Aerosol: The overall Mass median aerodynamic diameter (MMAD) and geometric standard deviation for salmeterol xinafoate were 2.35μm and 3.05. 84% of the particles were <7 μm.

Clinical Observations: None.

Body Weight Gained: F, LD, +52%, HD, +56%.

Food Consumption: No effect.

Ophthalmic Examination: No effect.

Hematology: Platelet Count, F, HD, -19%
Neutrophil Count, F, HD, +31%
Lymphocyte Count, F, HD, +31%

Clinical Chemistry: Glucose, HD, M, -21%, F, -23%.

Urinalysis: No effect.

Plasma Levels: At the LD very little salmeterol was detected in the plasma when determined 7.6- 13.6 min after dosing on day 1, weeks 4 and 13. At the HD, the mean plasma levels ± S.D.ng/ml for salmeterol were 15.4 ±4.8 ng/ml, 9.1 ±3.9 ng/ml and 7.4 ±1.5 ng/ml on day 1, weeks 4 and 13, respectively, indicating increased metabolism od salmeterol xinafoate upon repeated administration. This indication is tempered by increased sampling times as the study progressed (day 1, 7.6 ±3.2 min, week, 4, 14.8 ±4.1 min and week 13, 27.1 ± 7.0 min).

Necropsy

Organ Weight

Uterus, HD, Absolute, +49%; Relative weight change was not reported.

Macroscopic Findings: None.

Histopathology:

The results summarized in the following table show that pathological changes were seen in the laryngeal/pharyngeal areas and lungs with the M showing greater sensitivity. The F also manifested plasmacytosis in the cervical lymph node and uterine dilatation.

Organ/ Pathology	Incidence					
	M			F		
	C	LD	HD	C	LD	HD
Larynx/Pharynx						
Extension of Ventral Surface Epithelium Exhibiting Squamous Characteristics	0/12	0/12	4/12	0/12	0/12	0/12
Increase in the Area of Epithelium on the Inner Aspect of the Arytenoid Cartilages Showing Squamous Characteristic Frequently with Some Keratinization	0/12	2/12	3/12	0/12	2/12	2/12
Lungs						
Acute-Alveolar Acute Inflammatory Exudate	0/12	0/12	3/12	0/12	0/12	0/12
Lymph Node Cervical						
Plasmacytosis	0/12	0/12	0/12	1/12	0/12	4/12
Uterus						
Dilatation				1/12	3/12	5/12

Conclusion

Salmeterol administered daily by inhalation to rats for 13 weeks at doses of 0.07 and 0.64 mg/kg with an aged lactose powder mixture produced irritation in the respiratory tract particularly in the laryngeal/pharyngeal areas. Since the dose of GR97980X (0.0029 and 0.0033 mg/kg) and the incidence of irritation in each salmeterol xinafoate-treated group were similar, this suggests that the irritation to the laryngeal/pharyngeal areas was attributed to the degradant, GR97980X, and not to the salmeterol xinafoate. Other manifestations were apparently due to β_2 agonism, since they were dose related. These were increased body weight gain, hypoglycemia, increased uterine weight, decreased platelet count and increased neutrophil and lymphocyte count. At the HD, plasma levels of salmeterol decreased with time.

Salmeterol xinafoate and GR97980X (powder formulation): 13 Weeks inhalation toxicity study in dogs, No. D21268, vol. 5.1, p 1.

There was a signed GLP statement.

Study Site:

Study Dates: 3/25/96- 6/23/96

Method

Animals: 5 month old M and F (5.9 kg-10.9 kg) Beagle dogs were used: 4 M and 4 F/ group.

Compounds: Salmeterol xinafoate (5%, w/w Batch No. U96/015A) in lactose, Salmeterol xinafoate (5%,w/w Batch No. U96/017A +0.13% w/w GR97980X) in lactose, Salmeterol xinafoate (5%,w/w Batch No. U96/016A +0.33% GR97980X) in lactose, Salmeterol xinafoate (25 μg/ metered dose from 120 dose metered dose inhaler containing propellant P11/P12, Batch No. WO375GCA and Batch No. WO375GCA)

Route: Inhalation.

Doses: The following daily doses (base) were administered by inhalation via an oropharyngeal tube (concentration adjusted so that exposure time was 6 min) for 13 weeks.

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Group No.	Salmeterol xinafoate ug/kg/Day		GR97980X ug/kg/Day	
	Targeted	Estimated	Targeted	Estimated
1 (Lactose Control)	0	0	0	0
2 (MDI Salmeterol xinafoate)	16	18.0	0	0
3 (Salmeterol xinafoate in Lactose)	16	18.2	0	0
4 (Salmeterol xinafoate + Low Dose of GR97980X in Lactose)	16	18.1	0.42	0.37
5 (Salmeterol xinafoate + High Dose of GR97980X in Lactose)	16	18.6	1.07	1.00

The following parameters were determined.

Particle Size of Aerosol: Mass median aerodynamic diameter (MMAD) and geometric standard deviation were determined during weeks 1, 4, 9, and 12.

Clinical Observations: Daily.

Body Weight: Prior to and Weekly.

Food Consumption: Daily during pretest and daily post treatment.

Ophthalmic Examination: Once (-2 weeks) prior to initiation and on week 12 of study.

Electrocardiography: Once (-2 weeks) prior to initiation and during week 12 of study prior to dosing.

Hematology and Clinical Chemistry: Once prior to (-2 weeks) initiation and on weeks 4 and 12 of study. In moribund animals bone marrow was removed prior to post mortem and examined.

Urinalysis: Weeks 4 and 12.

Plasma Levels: 2 min and 4 h post dosing on days 1 and during weeks 5 and 13.

Necropsy

The following organs were examined macroscopically and weighed: adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, spleen, testes with epididymides, thymus and thyroid and parathyroid glands.

Histopathology: Several conventional organs were removed and preserved. The following organs were examined for histopathology: larynx, tracheobronchial lymph nodes, lungs (including peripheral parenchyma), pharynx and epiglottis and tracheal bifurcation.

Results

Particle Size of Aerosol: salmeterol xinafoate in powder, MMAD 1.7-1.8μm, geometric S.D. 2.29-2.31; GR97980X in powder, LD, 2.2 μm, HD, 2.3 μm, geometric S.D., LD, 2.25, HD, 2.19; Inhalable fraction, <7 μm, salmeterol xinafoate, 95%, GR97980X, 92%.

Clinical Observations: None.

Body Weight Gained: No effect.

Food Consumption: No effect.

Ophthalmic Examination: No effect.

Electrocardiography: No effect.

Hematology: No effect.

Clinical Chemistry: No effect.

Urinalysis: No effect.

Plasma Levels: Salmeterol was determined by liquid chromatography with tandem mass spectrometric detection. The lower limits of quantification for salmeterol was 0.5 ng/ml. No data was presented for GR97980X except that it did not interfere with the analysis for salmeterol. The results are shown in the following table. Data at the 4 h measurement were not presented since the mean plasma levels were always less than 2 ng/ml. The levels of salmeterol when given as MDI tended to be lower than when administered as a powder, and the F tended to show levels in most determinations to be higher than the M. Changes in the plasma levels in dogs receiving salmeterol alone were not different from the plasma levels of salmeterol of

dogs receiving salmeterol and GR97980X.

Group No.	0.03 h Mean Plasma Levels, ng/ml Day 1		Weeks 5		13	
	M	F	M	F	M	F
2 (MDI Salmeterol xinafoate)	9.1	6.5	7.7	7.6	4.8	4.0
3 (Salmeterol xinafoate in Lactose)	5.3	6.6	7.5	12.4	2.0	13.1
4 (Salmeterol xinafoate + Low Dose of GR97980X in Lactose)	9.4	12.2	10.4	14.8	<6.7	17.0
5 (Salmeterol xinafoate + High Dose of GR97980X in Lactose)	12.3	8.1	16.0	12.0	10.7	12.3

Necropsy

Organ Weight: Relative and Absolute: No effect.

Macroscopic Findings: None.

Histopathology: No changes.

Conclusion

Neither salmeterol (16 μg/kg) alone or with the degradant, GR97980X (0.37 and 1.0 μg/kg), were toxic especially to the respiratory tract when administered by the inhaled route as a dry powder. Plasma levels of salmeterol tended to be higher when administered as a lactose powder mixture than when administered by a metered dose inhaler.

Genotoxicity

Microbial mutagenicity assay on salmeterol xinafoate aged lactose blend, No. WPT/90/12, vol. 10, p 105.

GLP signed statement: Yes

Study Dates: 12/15/89-1/22/90.

Site the study was conducted: Glaxo Group Research Ltd, Hertforshire SG12 ODP, England

Method

Organisms: Salmonella typhimurium TA98, TA100, TA1535 and TA1537 and Escherichia coli WP2 uvrA (pKM101). Liver microsomal enzyme reaction mix (S9 mix) was prepared from AHA albino rats injected with phenobarbital and β-Naphthaflavone.

Test Compound: salmeterol xinafoate lactose (Batch No. LO219C86 (stored at 30 °C for 34 months at 75% relative humidity) and U89/345A (freshly mixture and stored at 4°C)). Analysis Batch No. LO219C86 stored at 30 °C for 34 months at 75% relative humidity contained 0.18% w/w salmeterol base; the salmeterol base contained 4.1% GR97980X. U89/345A (freshly mixture and stored at 4°C) had no detectable levels of GR97980X.

Solvent: Dimethylsulfoxide.

Positive Controls:

Organism	With S9, Conc. (μg/plate)	Without S9, Conc. (μg/plate)
Salmonella typhimurium		
TA98	2-Aminoanthracene, (2)	Hycanthone, (10)
TAI00	2-Aminoanthracene, (2)	Na azide, (2)
TA1535	2-Aminoanthracene, (5)	Na azide, (2)
TA1537	Neutral Red, (10)	ICR-191, (1)
Escherichia coli		
WP2uvrA	2-Aminoanthracene, (5)	ENNG, (1)

With each organism the tests were conducted twice in three quadruplicate for the test

compound and in duplicate for the positive controls. A positive response was not clearly stated. The data were analyzed for statistical significance using a one-sided 5% significance level. This reviewer interpreted a positive response was a consistent dose related increase in the number of revertant colonies.

Concentrations: 0.5, 1.5, 5, 15 and 50 mg/plate of the salmeterol xinafoate lactose blend in the presence and absence of S9 mix for each organism. Due to limited solubility higher concentrations could not be tested. The concentrations of salmeterol xinafoate and GR97980X tested in the assay based on the concentrations of the salmeterol xinafoate lactose are listed in the following table. The freshly salmeterol xinafoate lactose mixture containing no degradant was tested with the above concentrations in the presence and absence of S9 mix using only Salmonella typhimurium TA98 as the test organism.

Concentration of Salmeterol Xinafoate Aged Lactose Blend, mg/plate	Concentration of Salmeterol Base, μg/plate	Concentration of GR97980X μg/plate
0.5	0.9	0.0369
1.5	2.7	0.1107
5.0	9.0	0.369
15	27.0	1.107
50	90.0	3.69

Results

The salmeterol xinafoate aged blended lactose containing 4.1% of the degradant, GR97980X, did not consistently produced a dose related increase in the number of revertant colonies in the presence and absence of metabolic activation. The concentrations of salmeterol base tested ranged from 0.9 to 90 μg/plate; they contained concentrations of GR97980X that ranged from 0.0369 to 3.69 μg/plate. No mutagenic activity was noted with the fresh lactose mixtures at similar concentrations of salmeterol. The positive controls increased the number of revertant colonies more than threefold.

Conclusion

Concentrations (0.9 to 90 μg/plate) of salmeterol base as the xinafoate salt in aged lactose mixture containing 4.1% of the degradant, GR97980X, and salmeterol xinafoate fresh lactose mixture containing no degradant were not mutagenic in the bacterial assay.

OVERALL SUMMARY AND EVALUATION

This NDA was for administering salmeterol xinafoate by inhalation as a dry powder. This formulation consists of the β_2 agonist and lactose monohydrate, a commonly used excipient for dry powder inhalers. The Pharmacology and Toxicology of salmeterol xinafoate have been studied in depth. Attached is the review of the pharmacologic and toxicologic studies submitted in NDA 20-236 for aerosolized salmeterol xinafoate .

In the process of formulating this product, a degradant, GR97980X, was formed; this was caused by the condensation of salmeterol with hydroxynaphoic acid, the acid portion of salmeterol xinafoate. Since the sponsor proposes that the salmeterol dry powder product contains 3% GR97980X as the maximum upper limit, this was above the qualification threshold level of 1% according to the proposed Guidelines (Federal Register 61: 11268-11272, March 16, 1996). Consequently, pharmacologic and toxicologic studies were conducted on GR97980X to assess its β_1 and β_2 agonist properties and toxic potential.

Pharmacologic studies using the histamine-induced contraction of the isolated guinea pig trachea and spontaneous beating guinea pig right isolated atria showed GR97980X to be devoid of β_1 and β_2 agonist properties.

In humans salmeterol is extensively metabolized by aliphatic oxidation to the α-hydroxysalmeterol. Using human liver microsomes, it was found that the aliphatic oxidation was due predominantly to the P450 isoenzyme CYP3A4 and to a lesser degree to P450 CYP2E1. This indicates that patients on salmeterol should be cautioned in using drugs that inhibit these liver enzymes, i.e., ketoconazole or disulfuram. This may result in increased incidence of side effects as a consequence of increased levels of salmeterol.

In dogs, the major metabolite of salmeterol excreted in the bile follow p.o. administration was identified as is the 3-catechol sulfate of the benzoic acid derivative. Three minor metabolites were identified chromatographically; their structures were not defined.

In acute toxicity studies of the degradant, GR97980X, no toxicity was noted at p.o. doses up to 768 mg/kg in rats; by the inhaled route (ca 37 and 60 mg/kg) decreased body weight gained occurred only in the HD F. The respective p.o. and inhaled NOAELs were 768 and 37 mg/kg. Macroscopically, no organs were targeted.

In a 13-week inhalation study in rats, salmeterol was administered as a mixture in aged lactose powder. The MMAD was 2.35μm and more than 84% of the particle size was $<7\mu$m indicating that deposition was predominantly in the nasopharyngeal and pulmonary areas. Although the doses of salmeterol were 0.07 and 0.64 mg/kg, the doses of GR97980X administered with both doses of salmeterol in the powder formulation were similar, i.e., 0.0029 and 0.0033 mg/kg. Similar incidences (4/24 and 5/24) of extension of the squamous

epithelium frequently with keratinization on the inner aspect of the arytenoid processes indicative of irritation were seen in both groups. Thus, the degradant, GR97980X, was most likely responsible for the irritation to the respiratory tract since both the high and low dose salmeterol xinafoate-treated groups received similar doses of the degradant. The NOAEL for GR97980X was not established.

To confirm this irritant effect of GR97980X to the respiratory tract, a 13 week inhalation study using an oropharyngeal tube was conducted in dogs, a second species. This species was selected since the method of delivering inhaled drugs to dogs more closely resembles that in man, and respiratory disposition is comparable for dogs and humans. Salmeterol, 18.0-18.6 μg/kg, was administered alone by metered dose inhaler (MDI), as a dry powder in lactose or in combination with 0.37 and 1.0 μg/kg of GR97980X, the degradant, as a dry powder in lactose. As in the rat, the MMAD was 1.7-1.8 μm and more than 90% of the particle size for salmeterol and GR97980X was $<7\mu$m indicating that deposition was in the nasopharyngeal tracheal and bronchiolar areas. No local or systemic toxicity was noted; plasma levels were detected indicating that salmeterol was absorbed from the respiratory tract.

The anatomy of the respiratory tract of the dog is more closely to humans than to rats. Rats in contrast and humans are obligated nose breathers and due to the highly convoluted nasal passage possess high nasal filtering capacity. Further, the rats are more sensitive than primates since pharmaceuticals that produce changes in the respiratory tract in rats fail to consistently produce lesions in the respiraory tract of primates (Lewis, Toxicologic Pathology 19: 353-357, 1991). Consequently, the dog is apparently a more reliable species to predict respiratory toxicity of inhaled substances in humans.

The potential maximum daily clinical dose of GR97980X based on its 3% presence (upper limit) in salmeterol (2 μg/kg) is 0.06 μg/kg. In the 3 month dog inhalation study, the NOAEL was 1.0 μg/kg. Based on a generally accepted safety factor of 6 between humans and dogs, i.e., the dog is 6 x more sensitive than humans, daily inhalation doses up to 0.17 μg/kg for GR97980X are considered safe. The maximum daily dose of 0.06 μg/kg for GR97980X in humans is safe since it is approximately one third the safe dose determined from this dog inhalation toxicity study. Thus, the proposed specification of the degradant, GR97980X, in the drug product is acceptable.

In the bacterial mutagenicity assay, neither the salmeterol aged lactose mixture containing degradant, GR97980X, nor the fresh salmeterol lactose mixture free of this degradant were mutagenic. The concentrations of salmeterol (0.9 to 90 μg/plate) in the aged lactose mixture assayed contained 4.1% (0.0365 to 3.65 μg/plate) of the degradant.

Issue to be Discussed with and Considered by the Medical Officer

In vitro studies using human liver microsomes, salmeterol is metabolized by aliphatic

oxidation to the α-hydroxysalmeterol. Ketoconazole, an inhibitor of the P450 isoenzyme, CYP3A4, completely blocked and disulfuram, an inhibitor of the P450 isoenzyme, CYP2E1, partially blocked this metabolic pathway. Should this drug interaction between salmeterol and drugs that interfere with these P450 microsomal enzymes which may result in increased plasma levels of the salmeterol and possible increased adverse effects be incorporated in the label.

Labeling Issues

The following changes in the label regarding preclinical data are recommended. Deletions are highlighted with a ~~strikeout~~ and additions are highlighted in RED.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, and leiomyomas of the uterus and a dose-related increase in the incidence of cysts in the ovaries. A higher incidence of leiomyosarcomas was not statistically significant; tumor findings were observed at oral doses of 1.4 and 10 mg/kg, which gave approximately 9 and 63 times, respectively, the human exposure based on rodent:human AUC comparisons.

Salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts in Sprague Dawley rats in a 24-month inhalation/oral carcinogenicity study. Tumors were observed in rats receiving doses of 0.68 and 2.58 mg/kg per day [approximately 55 and 209 times the maximum recommended human daily inhalation dose on a mg/m^2 basis) These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

No significant effects occurred in mice at 0.2 mg/kg (approximately 1.3 times the maximum recommended human daily inhalation dose based on comparisons of the AUCs) and in rats at 0.21 mg/kg (approximately 17 times the maximum recommended human daily inhalation dose on a mg/m^2 basis).

Salmeterol xinafoate produced no detectable or reproducible increases in microbial and mammalian gene mutation *in vitro*. No clastogenic activity occurred *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus test.

No effects on fertility were identified in male and female rats treated orally with salmeterol xinafoate at doses up to 2 mg/kg orally approximately 162 times the maximum recommended human daily inhalation dose on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** No significant effects of maternal exposure to oral salmeterol xinafoate occurred in the rat at doses up to 2 mg/kg

(approximately 162 times the maximum recommended human daily inhalation dose on a mg/m^2 basis). Dutch rabbit fetuses exposed to salmeterol xinafoate *in utero* exhibited effects characteristically resulting from beta-adrenoceptor stimulation; these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at 0.6 mg/kg orally (approximately 12 times the maximum recommended human daily inhalation dose based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at 10 mg/ orally (approximately 1,600 times the maximum recommended human daily inhalation dose on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to use in humans.

OVERDOSAGE:

No deaths were seen at maximum practicable inhalation doses of 2.9 mg/kg in rats (approximately 235 times the maximum recommended human daily inhalation dose on a mg/m^2 basis) and 0.7 mg/kg in dogs (approximately 189 times the maximum recommended human daily inhalation dose on a mg/m^2 basis). By the oral route, nonlethal doses were 150 mg/kg in mice (approximately 6,000 times the maximum recommended human daily inhalation dose on a mg/m^2 basis) and 1,000 mg/kg in rats (approximately 81,000 times the maximum recommended human daily inhalation dose on a mg/m^2 basis).

RECOMMENDATION

This NDA is a new formulation for administering salmeterol by inhalation. The daily dose of the degradant formed in the preparation of this formulation is safe. From a preclinical standpoint, this NDA is approvable.

The suggested labeling revisions should be conveyed to the Sponsor.

The Medical Officer should consider the drug interaction between salmeterol and drugs that inhibit the P450 isoenzymes, CYP3A4 and CYP2E1 a labeling issue.

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Lawrence F. Sancilio 5/14/97

Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

May 14, 1997

NDA 20-692
cc. HFD 570/Division File
HFD 570/SJohnson
HFD 570/Poochikian
HFD 570/LFSancilio
HFD 570/CSO
HFD 570 /SUN
Attachment: Original Review of NDA 20-236 by L. F. Sancilio, 12/20/91

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Approved By C. Sun, Ph.D.

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