

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-692**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,692

Submission Date: June 18, 1996  
October 8, 1996

**Drug Name, Dose and Formulation:** Serevent MDPI Diskus (Salmeterol xinafoate) inhalation powder, 50 µg salmeterol (as xinafoate) per dose

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

**Reviewer:** Venkata Ramana S. Uppoor, Ph.D.

**Type of Submission:** New Drug Application, 3S

**BACKGROUND:**

Serevent Diskus contains salmeterol xinafoate which is a long-acting  $\beta$ -agonist used in the treatment of upper respiratory tract diseases mainly in mild to moderate asthma. Salmeterol is approved in U.S. as an oral inhalation aerosol (Serevent Inhalation Aerosol which is a CFC MDI). The sponsor has been developing 2 dry powder formulations for this drug, one is Serevent Rotadisk (Diskhaler) under \_\_\_\_\_ and the other being Serevent Multidose Powder Inhaler Diskus (MDPI) under IND 43,097. The sponsor \_\_\_\_\_

\_\_\_\_\_ wants to use the clinical data generated from the Diskhaler along with few other studies to support the approval of the NDA for the Diskus (MDPI). The agency agreed that this is acceptable provided the sponsor conducts a pharmacokinetic study to compare the plasma concentrations of salmeterol following Diskhaler and Diskus.

Serevent Diskus inhalation powder is a specially designed plastic device containing a double-foil blister strip of a powder presentation (60 blisters/strip) of salmeterol xinafoate intended for oral inhalation only. Each blister contains 50 µg of salmeterol as the xinafoate made up to 12.5 mg with lactose.

**II. OBJECTIVES**

This submission is an NDA to request approval for Serevent Diskus inhalation powder (50 µg bid) for the maintenance treatment of asthma and 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 treatment with inhaled, short-acting  $\beta_2$ -agonists.

**III. PHARMACOKINETIC / BIOAVAILABILITY STUDIES**

The pharmacokinetics of salmeterol have been studied following administration via Serevent MDI and Serevent Rotadisk. Studies conducted using Serevent MDI were previously submitted in the NDA for the MDI. Two PK studies conducted using Serevent Rotadisk (using the \_\_\_\_\_ lactose fill formulation) are submitted in this application. These will not be reviewed here since the formulations used are not relevant. A pivotal PK study comparing Serevent MDI, Serevent Rotadisk

(12.5 mg lactose fill formulation) and Serevent Diskus has been submitted as an amendment in October 1996. This review includes the study summary of the pivotal study SLGB1004 (given below) and sponsor's proposed labeling for this product (Attachment I).

**STUDY SUMMARY:**

**STUDY SLGB1004, report GCP/96/035: SINGLE DOSE PHARMACOKINETICS STUDY**

A STUDY TO COMPARE PEAK PLASMA CONCENTRATIONS OF SALMETEROL FOLLOWING SINGLE INHALED DOSES OF SALMETEROL XINAFOATE ADMINISTERED TO HEALTHY SUBJECTS BY METERED DOSE INHALER, DISKHALER AND DISKUS INHALER.

**Reference:** Volume 1 - 1 of submission date, October 8, 1996

**Investigator:**

**Study Location:**

**Objective:**

1. To compare the peak and time to peak plasma concentrations of salmeterol after administration of salmeterol xinafoate by the MDI, reduced-fill Diskhaler and final device Diskus inhaler.
2. A preliminary study (Part I) was performed to identify the appropriate sampling time schedule for the main study.

**Drug supply:**

Salmeterol inhaler 25 µg 200 dose MDI (batch # W0194MC)

Salmeterol reduced-fill Diskhaler 50 µg Rotadisks (batch # 002)

Salmeterol Diskus inhaler 50 µg 60 dose (batch # U95/328A).

**Study design:**

This study consisted of 2 parts. Part I was a single dose, open-label, one-period study with two subjects receiving 400 µg salmeterol administered by means of the MDI. Part II consisted of a single dose, open-label, randomized, 3-period crossover design with 12 subjects each receiving 200 µg salmeterol administered by means of MDI, reduced-fill Diskhaler and final device Diskus inhaler. The washout between the drug administrations was at least 6 days. 14 healthy volunteers (2 males in part I and 6 males and 6 females in part II) of age 18 - 50 years participated in the study.

The treatment administration was as follows: Both subjects in part I of the study received one single dose of 400 µg salmeterol xinafoate as 16 inhalations from a 25 µg per inhalation MDI. Subjects in part II received 3 single doses of 200 µg salmeterol xinafoate as:

- A. 8 inhalations from a 25 µg per inhalation MDI.
- B. 4 inhalations from a 50 µg per inhalation reduced-fill Diskhaler.
- C. 4 inhalations from a 50 µg per inhalation final device Diskus inhaler.

The MDI treatment was given at 30 second intervals during part II, while the dry powder treatments were given at 60 second intervals. Dosing was completed within 3.5 minutes in part II.

Blood was collected in part I at 0, 10, 15, 20, 30, 40 and 50 minutes and at 1, 1.5, 2, 3, 4, and 6 hours post-dose. Based on the results of this study, sampling times for part II were selected and blood was collected in part II at 0, 5, 8, 12, 15, 20, 30, 40 and 50 minutes and at 1, 2, and 3 hours post-dose. Plasma sample analysis was conducted using a validated LC/MS method to determine salmeterol concentrations.

Pharmacokinetic parameters,  $AUC_{last}$ ,  $C_{max}$  and  $t_{max}$  were derived using standard non-compartmental analysis. Log transformed  $AUC_{last}$  and  $C_{max}$  were analyzed using ANOVA allowing for the effects due to subject, period and treatment. The analysis of  $t_{max}$  was carried out using Wilcoxon signed rank test. 90% confidence intervals were also computed.

## Results:

**ANALYTICAL METHOD AND ASSAY PERFORMANCE:** Assay conducted by Dept. of Bioanalysis, Glaxo Wellcome, Beckenham, UK.

For Salmeterol:

Method used: \_\_\_\_\_

Range: \_\_\_\_\_

Linearity: Linear within the range, \_\_\_\_\_

QC sample levels: \_\_\_\_\_ ng/ml

Accuracy: \_\_\_\_\_

Precision: % CV range = \_\_\_\_\_

Specificity: Acceptable

LOQ: \_\_\_\_\_

The analytical method used is acceptable.

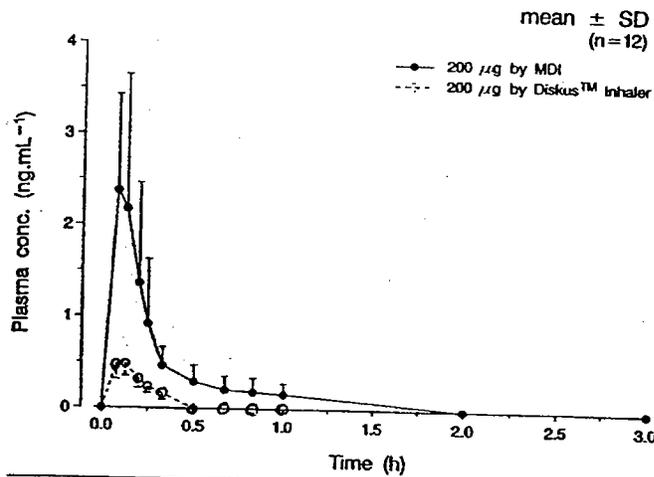
Results of part I showed that peak concentrations were achieved at the first sampling time of 10 minutes. Based on this, appropriate sampling time points for part II were selected.

Results of part II:

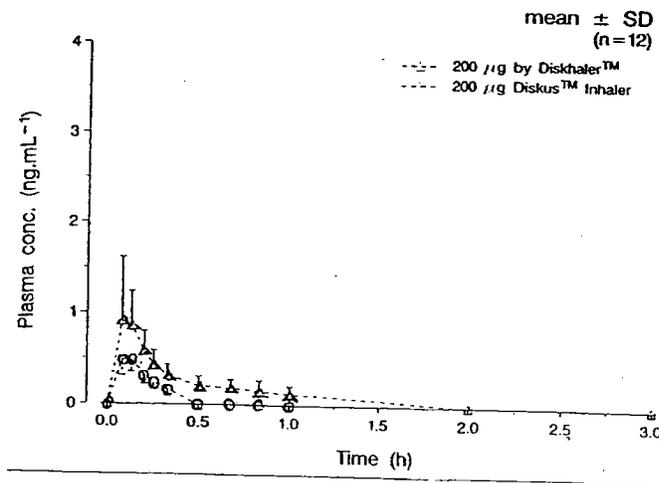
Mean PK parameters (and %CV), and 90% confidence intervals following single dose administration of salmeterol xinafoate via MDI, Diskhaler and Diskus are shown in the following table.

Parameters	Treatment	Arithmetic mean (%CV)	Ratio	Point estimate	90% C.I.
$C_{max}$ (ng/ml)	A: MDI	2.44 (55.7)	B/A	0.44	0.32 - 0.60
	B: Diskhaler	1.02 (67.2)	C/A	<b>0.26</b>	<b>0.19 - 0.36</b>
	C: Diskus inhaler	0.55 (28.1)	C/B	0.59	0.43 - 0.82
$AUC_{last}$ (ng.hr/ml)	A: MDI	0.752 (71.4)	B/A	0.58	0.38 - 0.89
	B: Diskhaler	0.394 (69.1)	C/A	<b>0.31</b>	<b>0.20 - 0.47</b>
	C: Diskus inhaler	0.225 (79.8)	C/B	0.53	0.35 - 0.81
$T_{max}$ (hr)		Median (range) for $T_{max}$	Diff.		
	A: MDI	0.08 (0.08 - 0.20)	B-A	0.00	
	B: Diskhaler	0.13 (0.08 - 0.13)	C-A	<b>0.00</b>	
	C: Diskus inhaler	0.11 (0.08 - 0.13)	C-B	0.00	

Mean plasma concentration-time curves of salmeterol following MDI, Diskhaler and Diskus are shown in the following figures:



● MDI  
○ DISKUS  
△ DISKHALER



CONCLUSION: Both  $C_{max}$  and  $AUC_{last}$  were significantly lower when salmeterol was given via dry powder formulations as compared to MDI.  $C_{max}$  and AUC was also significantly lower after administration of salmeterol from Diskus than the Diskhaler.  $T_{max}$ , however is comparable across all the three dosage forms. Terminal rate constant could not be calculated because of secondary peaks and absence of clear terminal phase in certain cases.

#### IV. COMMENTS TO THE MEDICAL OFFICER

Pharmacokinetics of salmeterol could not be determined due to low concentrations achieved following administration of salmeterol by inhalation. Although the assay methodology is quite sensitive with a limit of quantitation of —, the entire plasma concentration-time profile could not be characterized. However, it is still important from a safety perspective, to determine the peak plasma concentrations and compare to that of the currently marketed Serevent inhalation aerosol (MDI). The pivotal study SLGB1004 was carried out to compare the concentrations achieved with Diskus (final formulation), MDI and the Diskhaler. Results indicate that the peak concentrations and AUC of salmeterol achieved via Diskus are lower than those of MDI and Diskhaler. This indicates lower systemic absorption. Whether this is due to less deposition in lungs (which might lead to lower efficacy) or less deposition in the oropharyngeal region cannot be discerned from this study.

#### V. LABELING COMMENTS

Plasma concentrations mentioned in the label under a) the pharmacokinetics section and b) use in nursing mothers' section is not based on the pivotal study SLGB1004. This information is obtained from Diskhaler, not the Diskus. The labeling should be modified to include data obtained from study SLGB1004. This will reflect plasma concentrations achieved using the Diskus (product of this NDA).

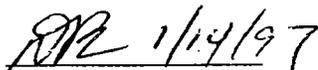
#### VI. RECOMMENDATION

This submission has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and is found to be acceptable. The systemic availability of salmeterol following administration via Serevent Diskus is lower than that of MDI and Diskhaler. Please forward the above labeling comment to the sponsor.

  
Venkata Ramana S. Uppoor, Ph.D.

Division of Pharmaceutical Evaluation-I

FT Initialed by Dale Conner, Pharm.D.

  
1/14/97

CC list:

HFD-570: NDA 20,692; HFD-570: Division file; HFD-570: CSOParinda Jani;  
HFD-570: Medical Reviewer\Susan Johnson; HFD-570: Chemist; HFD-570: Pharmacologist;  
HFD-870: Dale Conner; HFD-870: John Hunt; HFD-870: ChenMe; HFD-860: Marroum;  
HFD-850: Biopharm\Lesko; HFD-870: Chron; HFD-870: Drug; HFD-870: Reviewer;  
HFD-860: Venkata Ramana S. Uppoor; HFD-340: Viswanathan.

CM

14 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

JUL 10 1996

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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NDA 20,692

Submission Date: June 18, 1996

**Drug Name, Dose and Formulation:** Serevent MDPI Diskus (Salmeterol xinafoate) inhalation powder, 50 µg salmeterol (as xinafoate) per dose

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

**Reviewer:** Venkata Ramana S. Uppoor, Ph.D.

**Type of Submission:** New Drug Application, 3S

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**ISSUE:** 21-day Filing

**BACKGROUND:**

Serevent Diskus contains salmeterol xinafoate which is a long-acting  $\beta$ -agonist used in the treatment of upper respiratory tract diseases mainly in mild to moderate asthma. Salmeterol is approved in U.S. as an oral inhalation aerosol (Serevent Inhalation Aerosol which is a CFC MDI). The sponsor has been developing 2 dry powder formulations for this drug, one is Serevent Rotadisk and the other being Serevent Multidose Powder Inhaler Diskus (MDPI) under IND 43,097. The sponsor

wants to use the clinical data generated from the Rotadisk along with few other studies to support the approval of the NDA for the multidose powder inhaler product (MDPI).

Serevent Diskus inhalation powder is a specially designed plastic device containing a double-foil blister strip of a powder presentation (60 blisters/strip) of salmeterol xinafoate intended for oral inhalation only. Each blister contains 50 µg of salmeterol as the xinafoate made up to 12.5 mg with lactose.

**II. OBJECTIVES**

This submission is an NDA to request approval for Serevent Diskus inhalation powder (50 µg bid) for the maintenance treatment of asthma and 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 treatment with inhaled, short-acting  $\beta_2$ -agonists.

**III. PHARMACOKINETIC / BIOAVAILABILITY STUDIES**

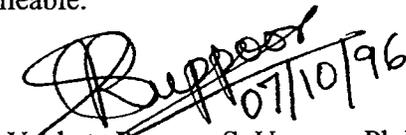
The pharmacokinetics of salmeterol have been studied following administration via Serevent MDI and Serevent Rotadisk. Studies conducted using Serevent MDI were previously submitted in the NDA for the MDI. Two PK studies conducted using Serevent Rotadisk (using the lactose fill formulation) are submitted in this application. A PK study comparing Serevent MDI, Serevent Rotadisk (12.5 mg lactose fill formulation) and Serevent Diskus is being conducted. The study report will be provided by the 4-month safety update. The summary table of studies submitted is provided in attachment I. The sponsor has also submitted the analytical method validation report.

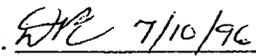
#### IV. COMMENTS

1. Studies to investigate the pharmacokinetics of salmeterol following administration via Serevent powder formulations have been conducted. Despite development of a sensitive analytical method (LC-MS assay with a LOQ of — pg/ml) for the assay of salmeterol, determination of the pharmacokinetic profile was not possible due to low salmeterol plasma concentrations. At the pre-NDA meeting, the agency requested the sponsor to carry out a PK study to compare the pharmacokinetics (at least the peak plasma concentrations) of salmeterol following administration via Serevent MDI, reduced fill Rotadisk (12.5 mg lactose) and to-be marketed Diskus. It was also stated at that time that the report could be submitted by the 4-month safety update. Hence, delayed submission of this study report is acceptable.
2. Information regarding metabolism of salmeterol is submitted in the Pharm/Tox section of this NDA. A copy of this study (Report WBP/93/062) investigating the specific enzymes responsible for the metabolism of salmeterol in human liver microsomes is needed for review.
3. It has been noted that device modifications, — of the device, have been made after the final PK study (on the Diskus). It may be a minor change, however, it may not be possible to assess the impact of these changes pharmacokinetically due to assay limitations. The chemist involved should look at this more closely to find out the impact of this change.

#### V. RECOMMENDATION

This submission has been reviewed for fileability by the Office of Clinical Pharmacology and Biopharmaceutics. This section of the NDA is organized, indexed, and paginated in a manner to initiate a substantial review. Hence, the submission is fileable.

  
Venkata Ramana S. Uppoor, Ph.D.  
Division of Pharmaceutical Evaluation II

FT Initialed by Dale Conner, Pharm.D. 

#### CC list:

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HFD-880: FleischerN; HFD-850: Biopharm\Lesko; HFD-870: Chron; HFD-870: Drug;  
HFD-870: Venkata Ramana S. Uppoor; HFD-340: Viswanathan; HFD-205: FOI.

# ATTACHMENT ①

Table 1: Biopharmaceutics Study Summary

Report Number Protocol Number Investigators Publications	Location Vol./Page	Route	Dosage Form(s) <sup>1</sup> Study Design	Dose	Batch Number (s)/ Plant/ Date Manufctd.	Number Treated Each Treatment/ Sex	Applicant (Sponsor) Conclusion
WB9/90/028 SLGT06 [See Footnote] N/A	11/57	Inhaled	L, Randomized, Double-Blind, Double- Dummy, Parallel Group	50mcg RD bid	U88/311A/ GOPS, Ware/ June, 1988	7 3M, 4F	Peak salmeterol plasma levels are detected in plasma 5 to 45 minutes after dosing. Steady state plasma concentrations are similar for the aerosol and powder formulations of salmeterol.
WB9/91/079 SLPT02 [See Footnote] N/A	12/1	Inhaled	O, L Randomized, Double-Blind, Parallel Group	25mcg RD bid 50mcg RD bid	U90/315A/ GOPS, Ware/ March, 1990  U90/316A/ GOPS, Ware/ March, 1990	20 20 26M, 14F	Plasma concentrations of salmeterol and HNA were similar to the results seen with adults; however, direct comparisons are difficult because samples were taken at different times post-dose in the pediatric and adult studies.
N/A SLGB1004 N/A	12/168	Inhaled	Part I - B Part II - B, H, P, Part I - Open Part II - Open, Randomized, Crossover	I - 400mcg MDI II - 200mcg MDI - 200mcg RD - 200mcg MDPI	W0194MC/ GOPS, Ware/ September, 1994  AX1670-002/ Laboratoires Glaxo, Evreux/ April, 1994  U95/328A/ GOPS, Ware/ September, 1995	NA	Data not available

RD = Rotadisk

<sup>1</sup> Product Code = See key at end of table.

WBP/90/028  
(SLGT06)

(\*\*Pharmacokinetic analysis conducted at Glaxo Group Research Limited (Greenford, UK). Refer to the SLGT06 listing in the controlled clinical studies section for a list of study sites.)

WBP/91/079  
(SLPT02)

(Pharmokinetic analysis conducted at Glaxo Group Research Limited (Ware, UK). Refer to the SLPT02 listing in the controlled clinical studies section for the list of study sites.)

**PRODUCT CODES**

- A Metered-dose inhaler 12.5mcg salmeterol/actuation
- B Metered-dose inhaler 25mcg salmeterol/actuation
- C Metered-dose inhaler 50mcg salmeterol/actuation
- D Metered-dose inhaler 100mcg salmeterol/actuation
- E Rotadisk 25mcg salmeterol in / lactose/blister, - Diskhaler
- F Rotadisk 50mcg salmeterol in / lactose/blister, - Diskhaler
- G Rotadisk 25mcg salmeterol in 12.5mg lactose/blister, - Diskhaler
- H Rotadisk 50mcg salmeterol in 12.5mg lactose/blister, - Diskhaler
- I Rotadisk 50mcg salmeterol in 12.5mg lactose/blister, - Diskhaler
- J Rotadisk 12.5mcg salmeterol in / lactose/blister, - Diskhaler
- K Rotadisk 25mcg salmeterol in / lactose/blister, - Diskhaler
- L Rotadisk 50mcg salmeterol in / lactose/blister, - Diskhaler
- M Rotadisk 100mcg salmeterol in / lactose/blister, - Diskhaler
- O Rotadisk 25 mcg salmeterol in 12.5 lactose/blister - Diskhaler
- P Multi-dose powder inhaler 50mcg salmeterol in 12.5mg lactose/blister
- Q Multi-dose powder inhaler 25mcg salmeterol in 12.5mg lactose/blister

**DIVISION OF PULMONARY DRUG PRODUCTS  
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA  
LABEL REVIEW**

**NDA 20-692**

**Reviewer:** Lawrence F. Sancilio, Ph.D.

**Date of Submission:** 6/18/96

**Date Completed:** 9/18/97

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

**Drug Name:** Salmeterol Hydroxynaphthoate (GR 33343G)  
Salmeterol xinafoate (Serevent Diskus Inhalation Powder)

**Chemical Name:** 4-Hydroxy- $\alpha^1$ -[[[6-(4-phenylbutoxy)hexyl) amino]-methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate

**Class:** B<sub>2</sub> Adrenoceptor Agonist

**Maximum Recommended Dose in Adults:** 50  $\mu$ g, twice daily, 2  $\mu$ g/kg, 74 $\mu$ g/m<sup>2</sup>.

**Indication:** Treatment of reversible bronchoconstrictive airway disorders

The following changes in the label regarding preclinical data are recommended. Original additions/changes are highlighted in **RED** and the new additions/changes are highlighted in **RED and BOLD**.

**Note:** Plasma levels in humans for the maximum therapeutic inhalation dose of salmeterol for this formulation was undetectable. Consequently, the AUC used for the maximum human therapeutic inhalation dose to determine the animal to human AUC ratio was from the metered dose inhaler formulation (NDA 20-236). With this formulation, levels of salmeterol were detectable to determine the AUC. Consequently, the ratio of animal AUC to the human AUC will not over estimate the ratio for the powder formulation of salmeterol.

2 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling