CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-692 S001/002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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Clinical Pharmacology & Biopharmaceutics Review

NDA 20-692/S-001, S-002
Salmeterol xinafoate inhalation powder Serevent® Diskus® Inhaler (50μg/inhalation)

Glaxo Wellcome
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Type of Submission:
Supplemental Applications
Submission Dates:
9/24/97
10/21/97

Reviewer:
Brad Gillespie, PharmD

Background: Salmeterol xinafoate is currently marketed in the U.S. as an inhalation aerosol (MDI) and dry powder inhaler (DPI). Both products are approved for treating reversible airway obstruction in patients ≥12 years of age. The MDI is also approved for the treatment of exercise induced bronchospasm (EIB). The maximum approved dose of salmeterol is 50 μg, twice daily. In these supplements, the sponsor is pursuing an EIB (S-001) and pediatric, age 4-11 (S-002) indication for its DPI. These supplements are primarily based on clinical safety and efficacy studies.

A formal pharmacokinetic program has not been conducted in support of the currently approved salmeterol products. No additional study reports were included in either of these submissions. Nevertheless, S-002 describes an ongoing pharmacokinetic/pharmacodynamic study designed to characterize drug-drug interactions between salmeterol and terfenadine or erythromycin. No preliminary data were provided in these submissions. As of the week of July 27, 1998, the final study report was not available for submission. The sponsor has agreed to provide these data in the final safety update prior to approval of the supplements.

In this review, all of the pharmacokinetic data obtained after administration of salmeterol via the Diskus formulation are summarized.

Adult Pharmacokinetic Data

Study SLGB 1004 was a single-dose, 3-arm crossover pharmacokinetic study in which 12 healthy subjects received 200 μg salmeterol via MDI, Diskhaler and Diskus formulations. Mean (%CV) salmeterol bioavailability parameters are described in Table 1. For further details, see Dr. R. Uppoor's 1/14/97 Clinical Pharmacology & Biopharmaceutics Review.

Table 1. Mean (%CV) Salmeterol Bioavailability Parameters After Administration of a Single 200 µg Dose

	C_{max} (ng/mL)	AUC (ng·hr/mL)	T_{max} (hours)[1]
MDI	2.44 (56)	0.75 (71)	0.08
Diskhaler	1.02 (67)	0.39 (69)	0.13
Diskus	0.55 (28)	0.23 (80)	0.11

Pediatric Pharmacokinetic Data

Study SLPT02 was a multi-center, multiple-dose, 3-arm (25 µg salmeterol, 50 µg salmeterol and 200 µg albuterol, all dosed twice daily as a dry powder) parallel group safety and efficacy trial with limited pharmacokinetic sampling after 3 months of dosing in the 25 and 50 µg salmeterol treatment groups. A total of 20 subjects (age 8-15 years, weight 19.5-69 kg) were randomized to each arm. One blood sample was collected from each subject between 1 and 7 hours after dosing. In the 25 µg group, 8 of 20 subjects had quantifiable plasma concentrations (pg/mL - pg/mL). In the 50 µg group, 11 of 20 had quantifiable plasma concentrations (pg/mL - pg/mL).

Comments

1. In the adult study, subjects received a single salmeterol dose of 200 µg. This is four times the maximum labeled single dose for this product. In the absence of dose proportionality information, it is impossible to predict what exposure would be at the clinical dose. Nevertheless, it is fair to assume that it would not exceed that observed after administration at the 200 µg level.
2. In the pediatric study it is unclear which dry powder device was used.
3. In the pediatric study, sufficient plasma samples were not collected to obtain meaningful pharmacokinetic data. Further, in the samples collected, inadequate quantifiable plasma levels were obtained to accurately estimate total salmeterol exposure or peak plasma concentrations.
4. The sponsor is reminded of their commitment to submit

[1] *Median (range)*

Recommendation The Office of Clinical Pharmacology & Biopharmaceutics has briefly reviewed the pharmacokinetic data available after administration of salmeterol dry powder to adult and pediatric populations. Based on the data submitted, it is not clear what the exposure at the clinical dose would be in either population. The adult estimate (at a dosage level 4 times the maximum clinical dose) would be acceptable for a conservative toxicokinetic comparison. Since there is inadequate pediatric pharmacokinetic data, approval of SEREVENT DISKUS for a pediatric population should be based entirely on clinical safety and efficacy trials. The drug-drug interaction trial will be reviewed when submitted.

Please forward Comment 4 to the sponsor.

/S/ 5/6/98

Bradley K. Gillespie, PharmD
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FT /S/ 08/18/98
Ramana Uppoor, PhD., Team Leader

cc: Sancilio
HFD-570 (NDA 20-692, Divisional File, Jani, Johnson)
HFD-870 (ChenME, Hunt, Uppoor)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)

APPEARS THIS WAY
ON ORIGINAL

		Placebo (N = 52)		Serevent Diskus (N = 52)	
0.5 hour post-dose exercise challenge	% fall in FEV_1	(N)	(% total)	(N)	(% total)
	< 10%	15	(29)	31	(60)
	≥ 10%, < 20%	3	(6)	11	(21)
	≥ 20%	34	(65)	10	(19)
Mean Maximal % fall in FEV_1 (SE)		- 25% (1.8)		-11% (1.9)	
8.5 hour post-dose exercise challenge	% fall in FEV_1				
	< 10%	12	(23)	26	(50)
	≥ 10%, < 20%	7	(13)	12	(23)
	≥ 20%	33	(63)	14	(27)
Mean Maximal % fall in FEV_1 (SE)		- 27% (1.5)		-16% (1.7)	

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Labeling