CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20983

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 18 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-983
Albuterol Sulfate Inhalation Aerosol
(90 μg albuterol base/inhalation)

SUBMISSION DATE:
06/30/98 (Serial No. N-000)
05/19/99

BRAND NAME: Ventolin HFA

SPONSOR: GlaxoWellcome

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Original NDA

Code: 3S

TITLE: "Review of Human Pharmacokinetics and Biopharmaceutics of an NDA"

BACKGROUND:

Previously, Ventolin (albuterol sulfate suspension) which delivers 90 μg albuterol base (ex-valve)/inhalation has been approved under NDA 18-473 by the Agency. It is available in a pressurized metered-dose inhaler (MDI) formulation for over 20 years. Ventolin is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older. The recommended dosing regimen is 2 inhalations repeated every 4 to 6 hrs (daily total being 720 to 1080 μg albuterol base).

SYNOPSIS:

On 06/30/98, GlaxoWellcome submitted an original NDA 20-983 (Serial No. N-000) seeking approval for Ventolin HFA (albuterol sulfate suspension) for oral inhalation. It delivers 120 μg albuterol sulfate from the valve (equivalent to 100 μg albuterol base) and 108 μg albuterol sulfate from the mouthpiece (equivalent to 90 μg albuterol base) per inhalation. On 05/19/99, an additional assay report was submitted to the above NDA.

Currently marketed Ventolin product contains oleic acid as excipient and CFC as propellant while Ventolin HFA MDI contains no excipients except HFA-134a as propellant, a non-CFC preparation, which reportedly will not damage the ozone layer. Due to low plasma albuterol levels achieved after therapeutic doses of albuterol after inhalation, little human pharmacokinetic (PK) data for albuterol is available. More recent developments in bioanalysis using

AUG 27 1998

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-983	**Type of Submission:**
Ventolin HFA (albuterol sulfate HFA-134a Inhalation Aerosol 120 µg/actuation: equivalent to 90 µg albuterol base from the mouthpiece)	NDA, 3S Suitability for Filing **Submission Date:** 06/30/98
GlaxoWellcome, Inc. P.O. Box 13398 Research Triangle Park, N.C. 27709	**Reviewer:** Brad Gillespie, PharmD

Background The active ingredient, albuterol sulfate (a relatively selective β_2-adrenergic bronchodilator) is formulated as a microcrystalline suspension in the propellant, HFA-134a. No surfactants, co-solvents or other propellants are employed. HFA-134a is a developed as a replacement for chlorofluorocarbons (CFC) which are believed to damage atmospheric ozone. At this time, HFA-134a is assumed to have no effect on the ozone layer. In support of this NDA, the sponsor has submitted data from 5 pivotal safety and efficacy trials as well as 8 clinical pharmacology and biopharmaceutics studies. Of these 8 trials, one compared a single 1.2 mg dose of Ventolin HFA to a single 1.2 mg dose of Ventolin CFC. The remaining 7 trials were designed to characterize the disposition of the propellant. The sponsor proposes that this product be indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older. The proposed dose is 2 inhalations every 4 - 6 hours.

In this review, the Human Pharmacokinetics section of the application will be reviewed to ensure that it is complete and is organized properly to permit a timely and efficient review.

Comments

1. Proposed package labeling is annotated to identify the source of labeling claims
2. The sponsor has conducted a single-dose study at approximately 6 times the proposed dose (1200 µg) to describe the disposition of the drug in human volunteers.
3. With regard to formulations, the pivotal pharmacokinetic and clinical safety and efficacy studies were conducted with the to-be-marketed product.
4. The sponsor has provided detailed assay performance data for the pivotal pharmacokinetic studies.

Discussion When reformulating an inhaled product, clinical efficacy and safety typically will need to be established independently of the currently approved product since these products usually work locally (in the case of inhaled albuterol, in the lungs). Thus, systemic exposure from inhaled products are usually not indicative of their efficacy. Nevertheless, some comfort with regard to safety can be obtained by comparing plasma

concentrations of the proposed product to that from an approved product at the clinical dose. If plasma levels observed are less than or equal to that of the approved product, it can be inferred that the proposed product is at least as safe systemically as the approved product. In keeping with this general philosophy, the sponsor was requested at a January 29, 1996 meeting between representatives of Glaxo Wellcome and FDA to conduct a small (n = 6-8), single-dose, 2-way crossover study comparing their proposed product to an approved albuterol product using a CFC propellant at the proposed dose of 200 μg. It was communicated to the sponsor that they should expect minimal albuterol concentrations near the limit of quantification. Nevertheless, they were told that if results were similar in both treatment arms, a waiver for evidence of *in vivo* bioavailability under 21 CFR 320.22 (e) could probably be granted for this product.

Alternatively, the sponsor has elected to conduct a single-dose bioequivalence study at a dose 6 times that proposed in the label. While at this dose level the pharmacokinetics of the product can be fully characterized, in the absence of dose proportionality information, it may not relate to drug disposition at the clinical dose. Therefore, this application should be considered as a stand alone NDA with regard to both safety and efficacy.

Recommendation The Human Pharmacokinetics section of this NDA has been briefly reviewed by the Division of Pharmaceutical Evaluation II for the purposes of filing and has been found to be complete and properly paginated to permit an efficient and timely review.

/S/ 8/27/98

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

/S/ 8/27/98

FT Ramana Uppoor, PhD., Team Leader

cc:
HFD-570 (NDA 20-983, Divisional File, Jani, Trontell)
HFD-870 (ChenME, Hunt, Uppoor)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)