CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-279

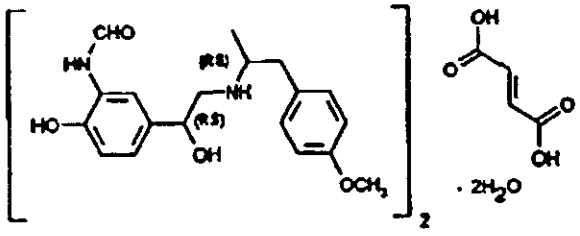
PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-279
Review number: #01
Serial number/date/type of submission:
Original Submission dated September 25, 2000
Amendment #000 BL dated July 26, 2001
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080
Manufacturer for drug substance: Same

Reviewer name: Timothy W. Robison, Ph.D.
Division name: Pulmonary and Allergy Drug Products
HFD #: 570
Review completion date: September 10, 2001

Drug:
Trade name: Foradil®
Generic name (list alphabetically): Formoterol fumarate
Code name:
Chemical name: ±2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl] formanilide fumarate dihydrate
CAS registry number: 45229-80-7
Mole file number:
Molecular formula/molecular weight: $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4.2H_2O$
Structure:



Relevant INDs/NDAs/DMFs:
NDA 20-831 Foradil Aerolizer
IND 34,342 Formoterol Fumarate (Foradil)

IND 47,013 Formoterol Fumarate (Foradil; Dry Powder Capsules)

DMF #
DMF #

Drug class: β_2-adrenergic receptor agonist

Indication: Chronic obstructive pulmonary disease (COPD)

Clinical formulation: Each clear, hard gelatin capsule contains a dry powder blend of 12 µg of formoterol fumarate and 25 mg of lactose as a carrier. The inactive ingredient of the capsules is gelatin.

Route of administration: Oral Inhalation

Proposed use: — bronchoconstriction in patients with — hronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

APPEARS THIS WAY
ON ORIGINAL

OVERALL SUMMARY AND EVALUATION:

Introduction:

Formoterol fumarate (Foradil®) is a β_2-adrenergic receptor agonist. Under NDA 20-831, Foradil® was approved for long-term, twice daily administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airway disease. The approved dose was 12 µg twice daily (24 µg total per day). As a Phase IV commitment, the sponsor agreed to conduct a large, simple, placebo-controlled post-marketing study to further evaluate the safety and efficacy of 24 µg twice daily (48 µg total per day). In the present application, Foradil® has been proposed for [redacted] bronchoconstriction in patients with [redacted] chronic obstructive pulmonary disease (COPD) [redacted] (24 [redacted] otal per day [redacted]). The sponsor submitted revised labeling dated July 26, 2001, which included dosing similar to that previously approved (i.e., 12 µg twice daily). Foradil® will be administered using an Aerolizer oral inhalation device.

All preclinical pharmacology and toxicology studies conducted with formoterol fumarate were reviewed under NDA 20-831 (see reviews dated June 1, 1998, March 13, 2000, April 25, 2000, April 26, 2000, April 27, 2000, and May 10, 2000; and a communication between Dr. Luqi Pei and Dr. Joseph DeGeorge, Chair of the Carcinogenicity Assessment Committee).

A safety concern with formoterol fumarate, common to β-adrenergic receptor agonists, is the potential for cardiac toxicity. Increased heart rates as well as clinical signs that included reddening of the mouth and ventral surface were evident in animals treated with formoterol by the oral or inhalation routes. Myocardial fibrosis was evident in male rats following inhalation exposure to formoterol at 400 µg/kg/day for 1 year. In contrast, myocardial fibrosis was evident in dogs following inhalation exposure to formoterol at a dose as low as 3 µg/kg/day for 1 month. The cardiotoxicity of β agonists appears to be a consequence of pharmacological activity related to increases of heart rate. Increased heart rate could be a consequence of direct interaction with β receptors in the heart, although, it was most likely a result of reflex tachycardia due to β_2-mediated vasodilation and hypotension. Ischemic changes (i.e., focal necrosis and fibrosis) occur in oxygen deprived regions of the heart. The papillary muscle in the left ventricle appears to be extremely sensitive to oxygen deprivation. If tachycardia were required for cardiotoxicity, no effect would be expected with doses that do not increase heart rate. Clinical experience suggests that inhaled doses ≤72 µg/day do not increase heart rate. Thus, appropriate safety margins appear to exist for clinical use of formoterol.

Four carcinogenicity studies were conducted with formoterol fumarate, drinking water and dietary studies in both mice and rats. In general, most of the tumor findings in these studies were judged to be pharmacological responses to β-adrenergic receptor agonists. Further, acceptable safety margins were established based upon AUC values for tumor findings in animals and the clinical dose (see review dated April 26, 2000).

In the present application, the Medical Officer has recommended that the maximum approved dose should not exceed 12 µg twice daily (24 µg total per day). This recommendation was reflected in the sponsor's revised labeling dated July 26, 2001. Thus, no changes in presently approved product labeling are required concerning Animal Pharmacology; Carcinogenesis, Mutagenesis, Impairment of Fertility; Pregnancy, Teratogenic Effects, Pregnancy Category C; Use in Labor and Delivery; or Overdosage.

Safety evaluation: Based upon reviews of preclinical pharmacology and toxicology studies conducted with formoterol fumarate under NDA 20-831, adequate safety margins appear to exist for clinical use as an inhalation drug product. From a preclinical standpoint, the application is approvable.

Safety issues relevant to clinical use: A safety concern with formoterol fumarate is the potential for cardiac toxicity. The cardiotoxicity of β agonists appears to be a consequence of pharmacological activity related to increases of heart rate. Clinical experience suggests that inhaled doses ≤72 µg/day do not increase heart rate. Thus, appropriate safety margins appear to exist for clinical use of formoterol.

Other clinically relevant issues: None.

Conclusions: From a preclinical standpoint, the application is approvable.

Communication review:

Labeling review: The Medical Officer has recommended that the maximum approved dose should not exceed 12 µg twice daily (24 µg total per day). This recommendation was reflected in the sponsor's revised labeling dated July 26, 2001. Thus, no changes in presently approved product labeling are required concerning Animal Pharmacology; Carcinogenesis, Mutagenesis, Impairment of Fertility; Pregnancy, Teratogenic Effects, Pregnancy Category C; Use in Labor and Delivery; or Overdosage.

RECOMMENDATIONS:

Internal comments: From a preclinical standpoint, the application is approvable.

External recommendations (to sponsor): None.

NDA issues: None.

Reviewer signature:

Timothy W. Robison, Ph.D. Date
Pharmacologist, HFD-570

Team leader signature [concurrence/non-concurrence]:

Timothy McGovern, Ph.D. Date
Acting Supervisory Pharmacologist, HFD-570

cc: list:
NDA 21-279, Division File, HFD-570
OstroffC, HFD-570
McGovernT, HFD-570
RobisonT, HFD-570

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Studies reviewed within this submission: All preclinical pharmacology and toxicology studies were reviewed under NDA 20-831.

Introduction and drug history:

Formoterol fumarate (Foradil®) is a β_2-adrenergic receptor agonist. Under NDA 20-831, Foradil® was approved for long-term, twice daily administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airway disease. The approved dose was 12 µg twice daily (24 µg total per day).

In the present application, Foradil® has been proposed for — — bronchoconstriction in patients with — chronic obstructive pulmonary disease (COPD).

All preclinical pharmacology and toxicology studies conducted with formoterol fumarate were reviewed under NDA 20-831.

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/s/

Timothy Robison
9/10/01 11:18:04 AM
PHARMACOLOGIST

Timothy McGovern
9/10/01 12:08:31 PM
PHARMACOLOGIST
I concur.

APPEARS THIS WAY
ON ORIGINAL