# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-592**

# PHARMACOLOGY REVIEW(S)

**PHARMACOLOGY AND TOXICOLOGY REVIEW**

**NDA #:** 21-592

**Product Name:** Foradil® Certihaler™ (Formoterol fumarate)

**Sponsor:** Novartis Pharmaceutical Corporation

**Indication:** Maintenance Treatment of Asthma

**Division:** Pulmonary and Allergy Drug Products

**Reviewer:** Timothy W. Robison, Ph.D.

**Date:** September 29, 2003

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# *EXECUTIVE SUMMARY*

## 1. Recommendations

1.1 Recommendation on approvability
From a nonclinical standpoint, the application is recommended for approval.

1.2 Recommendation for nonclinical studies
None.

1.3 Recommendations on labeling
The labeling for Foradil® Aerolizer™ has been generally retained for Foradil® Certihaler™; however, adjustments have been inserted to take into account differences in systemic drug exposure associated with the MDDPI as well as a different inhaled dose (i.e., 10 µg BID). Additional exposure data was provided and some adjustments were made to be in accordance with 21 CFR Part 201.57.

## 2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings

Nonclinical pharmacology and toxicology studies conducted with the active ingredient, formoterol, were extensively reviewed under NDA 20-831. A safety concern with formoterol, common to β-adrenergic receptor agonists, is the potential for cardiac toxicity. The cardiotoxicity of $\beta_2$ agonists appears to be a consequence of pharmacological activity related to increases of heart rate, which is monitorable in a clinical setting.

The multi-dose dry powder inhaler (MDDPI) drug product contains the excipient, magnesium stearate, which has been used extensively in oral drug products, but never in inhalation drug products. Thus, inhalation use of magnesium stearate is a safety concern in the evaluation of the MDDPI drug product. The second safety concern relates to potential changes of product performance (i.e., increased delivery of active ingredient).

To address concerns regarding the inhalational use of magnesium stearate, the sponsor conducted inhalation toxicology studies with this compound in rats and dogs. To address potential changes of produce performance, the sponsor conducted a 3-month bridging inhalation toxicity study in dogs to compare the new formulation (with magnesium stearate and lactose) and old formulation (with lactose).

Based upon the 6-month inhalation toxicology with magnesium stearate in rats as well as the GRAS status of magnesium stearate in foods and the

large ratio between safe oral doses and the proposed inhaled dose, the use of magnesium stearate as an inactive ingredient in the proposed drug product appears safe.

The sponsor conducted a 13-week bridging study with beagle dogs using the inhalation route to assess differences in the toxicity of a new formulation of formoterol with excipients, lactose and magnesium stearate, as compared to the older formulation of formoterol with lactose only. Toxicity profiles of the new and old formulations were comparable with particular reference to the heart in terms of heart rate, ECG findings, and histopathology. Plasma and urinary pharmacokinetic data indicated that systemic exposure to formoterol was increased by approximately 1.5 to 3.0-fold with the new formulation as compared to the old formulation. Based upon inhalation toxicology studies conducted with the formoterol dry powder in rats for periods ranging from 1 to 12 months, adequate safety margins appear to be present in adults and children based upon deposited dose.

2.2 Pharmacologic activity

Formoterol fumarate is a long-acting selective $\beta_2$-adrenergic receptor agonist. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. The pharmacologic effects of $\beta_2$ agonist drugs, including formoterol, are at least in part due to stimulation of intracellular adenylate cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle.

2.3 Nonclinical safety issues relevant to clinical use
None.

# *PHARMACOLOGY/TOXICOLOGY REVIEW*

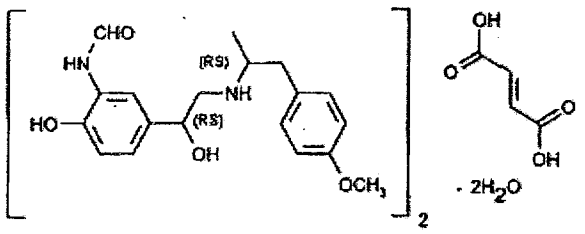
## 3.1 INTRODUCTION AND DRUG HISTORY

**NDA number**: 21-592
**Review number**: #01
**Sequence number/date/type of submission**:
#000/December 18, 2002/Initial Submission
**Information to sponsor**: Yes ( ) No (X)
**Sponsor and/or agent**: Novartis Pharmaceuticals Corporation
One Health Plaza
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 29, 2003

**Drug**:

Trade name: Foradil® Certihaler™
Generic name: 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
Molecular formula/molecular weight: $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$ / 840.9 g/mol
Structure:




**Relevant INDs/NDAs/DMFs**:
NDA 20-831 Foradil® Aerolizer™
NDA 21-279 Foradil® Aerolizer™
IND 34,342 Formoterol Fumarate (Foradil)
IND 47,013 Formoterol Fumarate (Foradil; Dry Powder Capsules) b(4)

IND 60,254 Formoterol Fumarate (Foradil, Metered-Dose Dry Powder Inhaler)
DMF # b(4)
DMF #

**Drug class**: $\beta_2$-adrenergic receptor agonist

**Indication**:
FORADIL CERTIHALER is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older, b(4) . It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting, beta$_2$-agonists.

b(4)

**Clinical formulation**:
The formulation consists of a white, free-flowing powder formoterol fumarate as the drug substance with lactose monohydrate and magnesium stearate as excipients. In dry powders for inhalation, the use of magnesium stearate is new. Assuming twice daily administration (i.e., BID), the daily dose of magnesium stearate is b(4)

The container used for the formoterol fumarate dry powder formulation is a multi-dose dry powder inhaler (MDDPI) designed to provide 60 device-metered doses for inhalation. The device is breath-actuated and equipped with a dose counter indicating the number of remaining doses. b(4)

Constructive provisions are taken to ensure dosing reproducibility from the reservoir and to prevent inadvertent double dosing or the return of an unused dose into the reservoir if no inhalation has taken place.

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Foradil 8.5 µg emitted dose (corresponding to 10 µg metered dose) MDDPI – Composition per emitted and per metered dose.

b(4)

**Route of administration**: Oral Inhalation

**Proposed use**: For adults and children 5 years of age and older, the usual dosage is one 10 µg Foradil inhalation every 12 hr. The total daily dose of Foradil should not exceed one inhalation twice daily (20 µg total daily dose).

**Disclaimer**: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Studies reviewed within this submission:**
1. Pharmacology.
2. Pharmacokinetics of formoterol in children (Aged 5-12 years, inclusive) that received 10 µg BID Foradil® by MDDPI (Study 0604).
3. Pharmacokinetics of formoterol in adolescents and adults that received 10 µg BID Foradil® by MDDPI (Study 2303).
4. Formoterol fumarate: Human UDP-Glucuronosyl Transferase mapping.
5. Four-week inhalation toxicology study with magnesium stearate in dogs.
6. Response to Division questions regarding the 13-week bridging toxicology study with dogs that was submitted under IND 60,254.

**Studies not reviewed within this submission**: None.

## 3.2 PHARMACOLOGY

### 3.2.1 Brief summary

Racemic formoterol at inhaled doses ≥0.14 µg/kg produced a dose-related inhibition of methacholine-induced bronchoconstriction in monkeys with an $ED_{50}$ of 0.2 µg/kg. Dose-dependent increases of heart rate were also evident. The effects of formoterol on methacholine-induced bronchoconstriction and heart rate appeared to be due to the activity of the R,R-enantiomer. For reviews of other pharmacology studies conducted with formoterol fumarate, refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

### 3.2.2 Primary pharmacodynamics

**Drug activity related to proposed indication:**

**Monkeys**

**Anti-Bronchoconstrictor and Cardiovascular Effects of Inhaled Formoterol in the Rhesus Monkey (Document number: RD-2002-03777):** Effects of racemic formoterol on methacholine-induced bronchoconstriction were examined in spontaneously breathing, anesthetized male rhesus monkeys. Body temperature, systolic and diastolic blood pressure, heart rate, oxygen saturation, and airway resistance were monitored continuously. Bronchoprovocation was induced by administration of inhaled methacholine. Racemic formoterol was administered by inhalation (nebulization) over a 10-min period at doses of 0.03, 0.14, 0.34, and 1.15 µg/kg. These are calculated deposited doses using a deposition factor of 30%. The dose of 0.03 µg/kg had no effects. Doses ≥0.14 µg/kg produced a dose-related inhibition of methacholine-induced bronchoconstriction with an $ED_{50}$ of 0.2 µg/kg. Maximal inhibition was observed at 5 min after the end of the 10 min drug treatment. Maximal effect (i.e., 75% inhibition) was observed with 0.34 µg/kg at 5 min and 1.15 µg/kg at 5 and 95 min. The duration of anti-bronchoconstrictor action was dose-dependent and loss of significance from control values was observed at 95, 155, and 275 min for 0.14, 0.34, and 1.15 µg/kg, respectively. A dose-dependent increase in heart rate was observed with a maximal effect of 27% observed with 1.15 µg/kg at 5 min after the end of drug administration. At each dose level, increased heart rate was sustained and significantly different from the control over the 270-min monitoring period after the end of drug administration. Blood pressure was not affected at any dose level.

**Anti-Bronchoconstrictor and Cardiovascular Effects of Inhaled R,R-Formoterol and S,S-Formoterol in Rhesus Monkeys (Document number: RD-1999-03167):** Effects of R,R-formoterol and S,S-formoterol, the active and inactive enantiomers, respectively, on methacholine-induced bronchoconstriction were examined in spontaneously breathing, anesthetized male rhesus monkeys. Body temperature, systolic and diastolic blood pressure, ECG, heart rate, oxygen saturation, and airway resistance were monitored continuously. Serum potassium levels were also monitored. Bronchoprovocation was induced by administration

of inhaled methacholine. Racemic formoterol (results from an earlier study), R,R-formoterol, and S,S-formoterol were administered by inhalation (nebulization) over a 10-min period at doses of 1.2, 0.56, and 0.54 µg/kg, respectively. These are calculated deposited doses using a deposition factor of 30%. R,R-formoterol and racemic formoterol inhibited methacholine-induced bronchoconstriction by 64 and 68%, respectively, at 15 min after the start of drug administration. Maximal effects (i.e., 71% inhibition for R,R-formoterol) were observed at 105 min after administration. Statistically significant inhibition of methacholine-induced bronchoconstriction for both drugs continued up to 165 min after the start of administration. Both R,R-formoterol and racemic formoterol increased heart rate by a maximum of 27% at 10 min after the start of administration. These significant increases of heart rate (i.e., ≥10%) persisted throughout the 280-min monitoring period. Blood pressure, respiratory rate, and serum potassium levels were not affected by either drug. S,S-formoterol had no effects on methacholine-induced bronchoconstriction, heart rate, blood pressure, or serum potassium concentrations. The effects of formoterol on methacholine-induced bronchoconstriction and heart rate appeared to be due to the activity of the R,R-enantiomer.

**Anti-Bronchoconstrictor Activities and Side Effect Potential of Inhaled Formoterol and (S,R)-Epiformoterol in the Rhesus Monkey (Document number: RD-2002-03717):** Formoterol contains two dissimilar chiral centers, which results in two possible diastereoisomeric forms and four possible enantiomeric configurations. Formoterol comprises the (R,R) and (S,S) enantiomeric forms of the like-diastereoisomer, and epiformoterol comprises the (R,S) and (S,R) enantiomeric forms of the unlike diastereoisomer. Effects of (S,R)-epiformoterol and racemic formoterol on methacholine-induced bronchoconstriction were examined in spontaneously breathing, anesthetized male rhesus monkeys. Body temperature, systolic and diastolic blood pressure, ECG, heart rate, oxygen saturation, and airway resistance were monitored continuously. Bronchoprovocation was induced by administration of inhaled methacholine. Racemic formoterol (results from an earlier study) or (S,R)-epiformoterol were administered by inhalation (nebulization) over a 10-min period at doses of 1.2 and 63 µg/kg respectively. These are calculated deposited doses using a deposition factor of 30%. Both racemic formoterol and S,R-epiformoterol inhibited methacholine-induced bronchoconstriction by 70-80% at 5 and 95 min after the end of drug administration. Significant inhibition by both agents (~50%) was still present at 155 min after the end of drug administration. Inhibition produced by racemic formoterol (i.e., 40%) was still present at 215 min. Both racemic formoterol and S,R-epiformoterol increased heart rate by a maximum of 27% at 5 min after the end of drug administration. These significant increases of heart rate (i.e., ≥10%) persisted throughout the 270-min monitoring period. Neither racemic formoterol nor S,R-epiformoterol had any effects on blood pressure. S,R-epiformoterol at 63 µg/kg was approximately equivalent to 1.2 µg/kg racemic formoterol in terms of inhibition of methacholine-induced bronchoconstriction and stimulating increased heart rate.

### 3.2.3 Secondary pharmacodynamics

Refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

### 3.2.4 Safety pharmacology

Refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

### 3.2.5 Pharmacodynamic drug interactions

Refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

## 3.3 PHARMACOKINETICS/TOXICOKINETICS

### 3.3.1 Brief summary

For children 5-12 years of age and adolescents/adults that received 10 µg BID Foradil® administered by multi-dose dry powder inhaler (MDDPI), systemic exposure to formoterol at steady state was 238 and 193.3 pmol·hr/L, respectively. Direct phenolic and aliphatic glucuronidation of formoterol is the primary metabolic pathway in humans. For reviews of other pharmacokinetic/toxicokinetic studies conducted with formoterol fumarate, refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

### 3.3.3 Absorption

**Humans**

**Pharmacokinetics of Formoterol in Children (Aged 5-12 years, inclusive) that received 10 µg BID Foradil® Delivered by the Multi-Dose Dry Powder Inhaler (MDDPI) (Study 0604).**

**Methods:** The sponsor conducted a Phase III multicenter, randomized, double-blind, parallel group trial designed to demonstrate the efficacy, safety, tolerability, and to evaluate the pharmacokinetics of 10 µg Foradil® administered twice daily (BID) by the MDDPI compared with placebo in male and female children aged 5-12 years with persistent asthma. The duration of the trial was 12 weeks. Pharmacokinetic data for week 4 are shown in the table below.

**Results:** For children 5-12 years old that received 10 µg BID Foradil® by MDDPI, systemic exposure to formoterol at steady state was 238 pmol·hr/L (Data for week 4).

Pharmacokinetic parameters of formoterol in children (5-12 years old) that received 10 µg BID Foradil® by MDDPI (Data for week 4).

| | $AUC_{0-12hr}$ pmol·hr/L | $CL_R$ (L/hr) |
|---|---|---|
| N | 8 | 8 |
| Mean | 238 | 13.38 |
| SD | 116 | 19.75 |
| Min | 84 | 1.72 |
| Median | 234 | 6.21 |
| Max | 419 | 61.68 |

**Pharmacokinetics of Formoterol in Adolescents and Adults that received 10 µg BID Foradil® Delivered by the Multi-Dose Dry Powder Inhaler (MDDPI) (Study 2303).**

**Methods:** The sponsor conducted a Phase III multicenter, randomized, double-blind, double-dummy, parallel group trial designed to demonstrate the efficacy, safety, tolerability and to evaluate the pharmacokinetics of 10 µg Foradil® administered twice daily (BID) by the multi-dose dry powder inhaler (MDDPI) compared with placebo and compared with albuterol 180 µg (QID) via pMDI in adolescent and adult patients with persistent asthma. The duration of the trial was 12 weeks. Pharmacokinetic data for week 12 are shown in the table below.

**Results:** For adolescents and adults that received 10 µg BID Foradil® by MDDPI, systemic exposure to formoterol at steady state was 193.3 pmol·hr/L (Data for week 12).

Pharmacokinetic parameters of formoterol in adolescents and adults that received 10 µg BID Foradil® by MDDPI (Data for week 12).

| | $AUC_{0-12hr}$ pmol·hr/L | $CL_R$ (L/hr) |
|---|---|---|
| N | 9 | 9 |
| Mean | 193.3 | 19.8 |
| SD | 105.6 | 12.0 |
| Min | 53.3 | 1.4 |
| Median | 187.7 | 18.4 |
| Max | 339.6 | 43.4 |

### 3.3.4 Distribution

### 3.3.5 Metabolism

**Formoterol Fumarate: Human UDP-Glucuronosyl Transferase Mapping (Document type: PCS(EU) R0101616).**

**Methods:** The objective of the present study was to identify the human UDP-glucuronosyl transferase (UGT) involved in the metabolism of formoterol using a human hepatocyte suspension from a single female donor, a human liver

microsomal pool of 21 donors, and microsomes from cDNA-baculovirus transfected insect cell lines expressing individual UGT isozymes. $^{14}$C-Formoterol was incubated with microsomes and hepatocyte suspensions. Metabolites were identified using radio-HPLC, LC-MS, and LC-MS/MS analyses.

**Results:** Direct phenolic and aliphatic glucuronidation of formoterol is the primary metabolic pathway in humans. Major radiolabeled peaks following incubation of $^{14}$C-formoterol with hepatocytes or a hepatic microsomal pool were phenolic (Ia) and aliphatic (Ib) glucuronides of formoterol. Phenolic glucuronidation ($Cl_{int}$ = 1.27 µL/min/mg) was more rapid than aliphatic glucuronidation ($Cl_{int}$ = 0.12 µL/min/mg). Glucuronides (IIa and IIb) of O-desmethyl-formoterol (II) were only found in incubations with hepatocytes. $^{14}$C-formoterol incubation with hepatocytes generated relatively more aliphatic glucuronides (Ib) than the human liver microsomal pool.

Incubations of formoterol with recombinant microsomes expressing single human UDP-glucuronosyl transferases were used to assess the involvement of 10 individual isoforms. Only UGT1A4 showed no formoterol glucuronidation activity. Formoterol phenolic glucuronidation (Ia) was catalyzed by all other isoforms examined (i.e., UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7, and 2B15). Formoterol aliphatic glucuronidation (Ib) was mediated by only three isoforms (i.e., UGT1A1, 1A9, and 2B7). The most active isoforms were UGT1A1, 1A8, 1A9, 2B7, and 2B15. UGT1A8 is not found in the human liver; however, it is found in the intestine.

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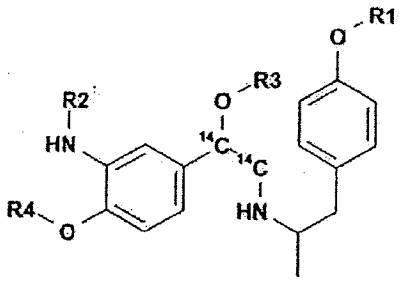
**Figure 10-2 Potential metabolites of $^{14}$C-formoterol**

Potential metabolites of $^{14}$C-formoterol as described by Rosenborg et al [Rosenborg et al 1999].




| Naming by: | | R1 | R2 | R3 | R4 | MH+ |
|---|---|---|---|---|---|---|
| Rosenborg et al | Novartis | | | | | |
| Formoterol (F) | Formoterol (I) | $CH_3$ | CHO | H | H | 349 |
| FG1 | Ia | $CH_3$ | CHO | H | $C_6H_9O_6$ | 525 |
| FG2 | Ib | $CH_3$ | CHO | $C_6H_9O_6$ | H | 525 |
| Met1 | II | H | CHO | H | H | 335 |
| Met2 | | $CH_3$ | H | H | H | 321 |
| FS | | $CH_3$ | CHO | H | $SO_3H$ | 429 |
| Met1G1 | IIa | H | CHO | H | $C_6H_9O_6$ | 511 |
| Met1G2 | IIb | H | CHO | $C_6H_9O_6$ | H | 511 |
| Met2G1 | | $CH_3$ | H | H | $C_6H_9O_6$ | 497 |
| Met2G2 | | $CH_3$ | H | $C_6H_9O_6$ | H | 497 |
| Met1S | | H | CHO | H | $SO_3H$ | 415 |
| Met2S | | $CH_3$ | H | H | $SO_3H$ | 401 |

$C_6H_9O_6$: Glucuronic acid moiety

### 3.3.6 Excretion

Refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

### 3.3.7 Pharmacokinetic drug interactions

Refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

### 3.3.10 Tables and figures to include comparative TK summary

For beagle dogs, administration of formoterol fumarate with magnesium stearate and lactose generally resulted in greater delivery of formoterol (i.e., improved product performance) as compared to formoterol fumarate with lactose. Clinical data appeared to indicate a similar pattern (data not shown).

Toxicokinetic parameters in dogs for formoterol administered with lactose and magnesium stearate (new formulation) or lactose alone (old formulation).

| Dose, µg/kg | Species | $AUC_{0-24hr}$, (nmol/L)·hr | |
|---|---|---|---|
| | | New formulation | Old formulation |
| 30 | Male dog (Day 12) | 65.2 | 43.4 |
| 30 | Male dog (Day 92) | 77.4 | 48.1 |
| 30 | Female dog (Day 12) | 52.5 | 34.3 |
| 30 | Female dog (Day 92) | 39.5 | 73.1 |

## 3.4 TOXICOLOGY

### 3.4.1 Overall toxicology summary

General toxicology:

Nonclinical toxicology studies conducted with the active ingredient, formoterol, were extensively reviewed under NDA 20-831.

In inhalation toxicology studies ranging from 1 to 12 months in duration, rats received formoterol using a dry powder formulation. For the 6/12-month study, target organs of toxicity were the testes, spleen, salivary gland, nasal cavity, lungs, and heart. A NOAEL was identified in this study and there is an appropriate safety margin to the clinical dose.

In inhalation toxicology studies ranging from 1 to 12 months in duration, dogs received formoterol using a dry powder formulation. In all studies, the heart was identified as the target organ of toxicity. Histopathological findings in the heart consisted of myocardial fibrosis. In general, NOAELs were not identified in inhalation toxicology studies with dogs. Clinical development of formoterol was allowed to proceed despite these findings in dogs. Toxic effects in dogs were attributed primarily to increased heart rate. In a clinical setting, heart rate can be monitored.

In the initial IND submission for MDDPI formulation of formoterol, the sponsor provided 1- and 6-month inhalation toxicology studies with magnesium stearate in rats. In a subsequent amendment, the sponsor provided a 3-month bridging inhalation toxicology study conducted in dogs. In response to a Division request for justification of species selection for the 6-month toxicology study with magnesium stearate, the sponsor provided a 28-day inhalation toxicology study with magnesium stearate in dogs in a later amendment.

In a 1-month inhalation toxicology study, 5 Wistar rats/sex/group were exposed to magnesium stearate at doses of 0 or 258 µg/kg/day. The MMAD for magnesium stearate was 0.92 µm. Using a deposition factor of 0.1, deposited

doses for magnesium stearate were 0 and 26 µg/kg/day, respectively. Administration of magnesium stearate to rats at a deposited dose of 26 µg/kg/day did not result in any treatment-related findings. The NOAEL for magnesium stearate was tentatively identified as 26 µg/kg/day given the small number of animals per group used in this study.

In a 28-day inhalation toxicology study, beagle dogs were exposed to magnesium stearate at doses of 0, 0.1, 1.9, and 36.8 mg/kg/day. Using a deposition factor of 0.17, deposited doses were estimated to be 0, 0.02, 0.3, and 6.3 mg/kg/day, respectively. The NOEL was 0.3 mg/kg/day. The dose of 6.3 mg/kg/day might be considered a NOAEL given the low incidence of histopathological findings at this dose and the uncertainty of the relationship of these findings to treatment. Histopathology findings were observed in lung, heart, kidneys, adrenals, and duodenum of dogs in the high dose group at the end of the 4-week treatment period. Given the low incidence of most of these findings (i.e., 1 of 6 dogs), relationships to treatment were unclear. Findings in the lungs at the high dose consisted of exudate containing foamy macrophages in bronchioles for 2 of 6 dogs as well prominent bronchial-associated lymphoid tissue for 1 of 6 dogs. These findings may be indications of local toxicity related to the inhalation of magnesium stearate. These findings may be of nonspecific nature associated with inhalation of high concentrations of dust. These findings were not evident at the end of the 4-week recovery period.

In a 6-month inhalation toxicology study, 10 Wistar rats/sex/group were exposed to magnesium stearate at doses of 0, 9.3, 200, 600, and 1800 µg/kg/day. The MMAD for magnesium stearate ranged from 0.86 to 1.52 µm. Using a deposition factor of 0.1, deposited doses of magnesium stearate were 0, 0.9, 20, 60, and 180 µg/kg/day, respectively. Administration of magnesium stearate at deposited doses ≤180 µg/kg/day did not result in any treatment-related findings. The NOAEL for magnesium stearate in rats was identified as 180 µg/kg/day. The sponsor provided no rationale for the selection of the rat.

The sponsor conducted a 13-week bridging study with beagle dogs using the inhalation route to assess differences in the toxicity of a new formulation of formoterol with excipients, lactose and magnesium stearate, as compared to the older formulation of formoterol with lactose only. Deposited doses of formoterol for the new formulation with the low, mid, and high dose groups were 0.5, 1.7, and 5 µg/kg/day, respectively. The deposited dose for the old formulation was 3.3 µg/kg/day. There were no differences in the toxicity profiles between the new and old formulations of formoterol. The deposited formoterol dose of 0.5 µg/kg/day for the new formulation could be considered the NOAEL given the sporadic nature of electrocardiographic changes and no histopathological findings at this dose. The dose of magnesium stearate at the NOAEL was 1 µg/kg/day. Control animals received a deposited dose of magnesium stearate at 9.7 µg/kg/day with no evident adverse findings. Electrocardiographic examinations found that heart rate was increased for male and female treatment groups receiving the new

formulation (low, mid, and high doses) and old formulation. Decreased Q-T and P-Q intervals as well as increased P wave amplitudes were also observed and probably associated with increased heart rates. Incidences of altered T wave polarity were increased in a dose-related manner, and were particularly predominant for the new formulation at the high dose and the old formulation. Increased heart rate may be attributed to either stimulation of cardiac $\beta_1$-receptors or a compensatory response to $\beta_2$-receptor-mediated peripheral vasodilation. There were no apparent treatment-related target organs of toxicity, although, papillary muscle fibrosis of the heart was observed for 1 male dog that received the new formulation at the mid dose. Plasma AUC values for formoterol in male and female dogs that received the new formulation at the high dose were, in general, approximately 1.5 times the values observed in male and female dogs that received the old formulation, possibly reflecting the same proportional difference in deposited dose. Quantities of formoterol excreted in urine for male and female dogs that received the new formulation at the high doses were approximately 2 to 3 and 1.5 times quantities excreted by male and female dogs that received the old formulation, respectively.

### 3.4.2 Single-dose toxicity

Refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

### 3.4.3 Repeat-dose toxicity

**Study title**: **Magnesium Stearate: 4 Week Repeat Dose Inhalation Toxicity Study in Dogs.**

**Key study findings**:

► The NOEL was 0.3 mg/kg/day. The dose of 6.3 mg/kg/day might be considered a NOAEL given the low incidence of histopathological findings at this dose and the uncertainty of the relationship of these findings to treatment.

► Histopathology findings were observed in lung, heart, kidneys, adrenals, and duodenum of dogs in the high dose group at the end of the 4-week treatment period. Given the low incidence of most of these findings (i.e., 1 of 6 dogs), relationships to treatment were unclear.

► Findings in the lungs at the high dose consisted of exudate containing foamy macrophages in bronchioles for 2 of 6 dogs as well prominent bronchial associated lymphoid tissue (BALT) for 1 of 6 dogs. These findings may be indications of local toxicity related to the inhalation of magnesium stearate. Further, these may be nonspecific findings associated with inhalation of dust. These findings were not evident at the end of the 4-week recovery period.

**Study no.**: CHS 57/942504
**Volume #, and page #**: Volume 1.6, Pages 1-154

**Conducting laboratory and location** [redacted] b(4)

**Date of study initiation**: October 22, 1993
**GLP compliance**: Yes.
**QA report**: yes (X) no ( )
**Drug, lot #, and % purity**: Magnesium stearate, Batch 91/0272

**Methods**
*Doses:* Estimated doses of magnesium stearate administered to dogs by inhalation were calculated with the following formula:

$$\text{Dose (mg/kg)} = \frac{\text{C (mg/L)} \times \text{RMV (L/min)} \times \text{F}}{\text{BW (kg)}}$$

C = concentration of magnesium stearate (mg/L)
RMV = volume of air inhaled in 1 min
D = duration of exposure per day
F = inhalable fraction (% <6 µm)
BW = body weight, kg

Inhaled and deposited doses

| Group | Mean aerosol concentration, mg/L | | Exposure time (min) | BW, kg | | Minute volume, L/min | | Inhaled dose[2], mg/kg/day | | Deposited dose[3], mg/kg/day | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Chamber | Face Mask[1] | | M | F | M | F | M | F | M | F |
| 2 | 0.029 | 0.017 | 15 | 9.4 | 9.3 | 5.54 | 4.59 | 0.122 | 0.102 | 0.02 | 0.02 |
| 3 | 0.25 | 0.15 | 30 | 8.6 | 9.1 | 4.01 | 5.22 | 1.70 | 2.09 | 0.29 | 0.36 |
| 4 | 2.43 | 1.41 | 60 | 8.8 | 8.9 | 4.90 | 4.60 | 38.2 | 35.4 | 6.49 | 6.02 |

1. The aerosol concentration was estimated at 58% of that obtained from the aerosol conditioning chamber.
2. On average, 81% of the magnesium stearate aerosol was < [redacted] µm equivalent aerodynamic diameter and considered to be respirable. It was not possible to calculate a MMAD ± GSD given that the particle size distribution of magnesium stearate was non log-normal. There appeared to be two distributions of particles for magnesium stearate aerosol. Most of the material was collected on stages 5 and 6 of the sampler indicating an aerodynamic equivalent diameter of [redacted] µm There was a subpopulation of particles (7.6-14.0% of the total collected) of aerodynamic diameter less than [redacted] µm (i.e., trapped on the final filter stage of the sampler. b(4)
3. A deposition factor of 0.17 was used to calculate the deposited dose.

Particle size distribution of magnesium stearate in Groups 2, 3, and 4 from weeks 1-4. Percent of total collected on each stage of the cascade impactor.

| Groups 2-4 | Stage 3 | Stage 4 | Stage 5 | Stage 6 | Stage 7 | Stage 8 | Filter | Respirable Fraction % < 1m |
|---|---|---|---|---|---|---|---|---|
| | 5.6% | 13.6% | 41.7% | 23.1% | 4.9% | 1.2% | 9.9% | 81% |

b(4)

*Species/strain:* Male and female beagle dogs were obtained from

b(4)

*Number/sex/group or time point (main study):* 3 dogs/sex/group were sacrificed following a 4-week treatment period.

*Route, formulation, volume, and infusion rate:* Inhalation. The exposure system consisted of a dust generator, an aerosol conditioning chamber, aerosol distribution subchamber, collapsible aerosol reservoir, and a face mask that was placed over the nose and mouth.

*Satellite groups used for toxicokinetics or recovery:* The control and high dose groups had 2 dogs/sex/group for a 4-week recovery period following the treatment period.

*Age:* At the start of treatment, dogs were approximately 4 months old.

*Weight (nonrodents only):* At the start of treatment, the body weight range for male and female dogs was 6.4 to 9.7 kg.

Unique study design or methodology (if any): Dose selection was based upon a preliminary inhalation toxicity study with magnesium stearate in dogs ( Project number 311736). Group 1, consisting of 1 dog/sex, was exposed to magnesium stearate at escalating inhaled doses of 0.168, 1.648, 3.29, and 10.01 mg/kg/day on days 1, 2-4, 5, and 6-9, respectively. Groups 2 and 3, each consisting of 1 dog/sex, were exposed to magnesium stearate at inhaled doses of 3.35 and 0.038 mg/kg/day, respectively, for 14 days. Deposited doses for Groups 2 and 3 were estimated to be 0.67 and 0.008 mg/kg/day, respectively. Magnesium stearate was administered with the use of an oropharyngeal tube, which differs from the 4-week inhalation toxicology study where a face mask was used. A concurrent control group was not included in this preliminary study. The female dog in Group 2 lost 11% of its body weight over the 14-day exposure period, which was associated with a significant decline in food consumption. On day 11 before dosing, minute volume and tidal volume for dogs in Group 2 were reduced to 50.3 and 49.8% of pretest values (4000-6000 mL/min and 250-325 mL), respectively. On day 11 before dosing, minute volume and tidal volume for the male dog in Group 3 were reduced to 86.8 and 79.5% of pretest values (3500 mL/min and 200 mL), respectively. Histopathological examination of lungs revealed the presence of eosinophilic foreign bodies for the female of Group 1 and both dogs of Group2. These foreign bodies, which may have been an agglomeration of test particles, displayed a polymorphic/crystalloid structure and were not associated with any reactive change. The female in Group 2 was diagnosed with acute hepatitis, purulent proctitis, and acute lymphadenitis of the mesenteric, retropharyngeal, iliac, and pancreatic lymph nodes.

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**Observation times and results**

Mortality: None.

Clinical signs: There were no treatment-related clinical signs.

Body weights (weekly): There were no treatment-related effects on body weight gain.

Body weights for male dogs in control, low dose, mid dose, and high dose groups at week 4 were increased by 17.2, 18.8, 22.1, and 20% of body weights on day 0, respectively. Body weights for female dogs in control, low dose, mid dose, and high dose groups at week 4 were increased by 17.7, 16.3, 16.7, and 18.5% of body weights on day 0, respectively. Body weight gains for male and female dogs of the control and high dose groups during the recovery period were comparable.

Food consumption (measured daily and calculated weekly): There were no treatment-related effects on food consumption.

Ophthalmoscopy (pretreatment and week 4 of treatment): Ophthalmic examinations were conducted for all dogs prior to the start of treatment and during week 4. There were no treatment-related ophthalmic effects.

EKG: Electrocardiograms were recorded for all dogs prior to the start of treatment and prior to dosing on one day during week 4. Electrocardiographic measurements consisted of standard limb leads I, II, and III, augmented limb leads aVR, aVL, and aVF, and unipolar chest leads CV5RL and V10. The sponsor reported that there were no treatment-related effects on electrocardiographic parameters, although, no data was provided for independent verification. The recording time appears to be inadequate given that measurements should be conducted at the approximate $T_{max}$.

Respiratory parameters: Tidal volume, respiratory rate, and respiratory minute volume were determined for all dogs twice prior to the start of treatment and during weeks 2 and 4 of the treatment period. There were no significant treatment-related effects on tidal volume, respiratory rate, and respiratory minute volume.

Hematology (pretreatment and during weeks 2 and 4 of treatment; values were combined for male and female dogs at each dose level except where noted): Reticulocyte percentages were increased for the mid and high dose groups during week 2 and all treatment groups during week 4. Other changes appeared to have little or no toxicological significance.

Week 2: Reticulocyte percentages for dogs at the mid and high doses were increased to 175 and 200% of the control (0.4%), respectively. Lymphocyte

counts for male treatment groups were decreased to 54.8-84.9% of the control (5.89 x $10^3/mm^3$), although, there was no evidence of a dose-response relationship. Mean corpuscular hemoglobin concentration (MCHC) for dogs at the high dose was slightly decreased to 97.6% of the control (32.6%), respectively. Prothrombin time for dogs at the high dose was slightly decreased to 93.9% of the control (6.5 sec).

Week 4: Reticulocyte percentages for dogs at the low, mid, and high doses were increased to 150, 275, and 200% of the control (0.4%), respectively. MCHC for dogs at the high dose was decreased to 96.7% of the control (30.7%).

Clinical chemistry (pretreatment and during weeks 2 and 4 of treatment): There were a number of small changes in clinical chemistry parameters, which appeared to have no toxicological significance.

Week 2: Cholesterol levels for female treatment groups were increased to 110.3-121.5% of the control (107 mg/dL), although, there was no dose response relationship.

Week 4: Potassium levels for male dogs at the high dose were increased to 110% of the control (4.0 mEq/L). Albumin levels for female dogs at the high dose were decreased to 92.3% of the control (2.6 g/dL). Cholesterol levels for male dogs at the mid and high doses were decreased to 76.1 and 88.8% of the control (134 mg/dL), respectively. Cholesterol levels for female treatment groups were increased to 112.5-128.9% of the control (104 mg/dL), although, there was no dose response relationship.

There were "apparent" elevations of alkaline phosphatase activity for female dogs at the high dose during week 2 and 4. However, during the pretreatment period, AP activity for control females was at a comparable level (424 mU/mL). Further, AP activity for female dogs at the high dose was comparable between the pretreatment period and weeks 2 and 4 of the treatment period. These "apparent" alterations of AP activity had no relation to treatment and observed levels were within the historical control range.

Urinalysis (pretreatment and during weeks 2 and 4 of treatment): There were no toxicologically significant changes of urinalysis parameters.

Gross pathology: At the end of the 4-week treatment period, findings were observed in the lung, heart, and duodenum for dogs in the high dose group. Given the low incidence of each finding (i.e., 1 of 6), relationships to treatment were unclear. These changes generally appeared to correlate with histopathological findings.

The finding for the lung consisted of an area of collapse at periphery of the apical lobe for 1 male dog in the high dose group. At the end of the 4-week

recovery period, multiple areas of firm dark red coloration were observed in all lobes except the right diaphragmatic lobe.

Findings for the heart consisted of slight yellow coloration in the ventricle above the papillary muscle for 1 male dog in the high dose group and right atrioventricular valve hemocyst for another male dog in the high dose group. At the end of the 4-week recovery period, right atrioventricular valve hemocyst was observed for 1 female dog in the high dose group.

The finding for the duodenum consisted of a dark red raised mucosal foci for 1 female dog in the high dose group.

Organ weights: Small changes of heart, lung, spleen, thymus, thyroid, and uterus weights were evident for dogs in the mid and/or high dose groups at the end of the treatment period. There were no histopathological correlations to these changes. Further, these organ weight changes were not evident at the end of the recovery period, suggesting that any changes were reversible.

Heart: Absolute and adjusted heart weights for male dogs at the high dose were increased to 106.0 and 124.1% of the control (63.3 and 58.0[A] g), respectively.

Lung: Adjusted lung weights for male and female dogs combined at the high dose were increased to 106.2% of the control (99.4[A] g).

Spleen: Absolute and adjusted spleen weights for male and female dogs combined at the high dose were increased to 108.4 and 123.2% of the control (58.1 and 55.3[A] g), respectively.

Thymus: Adjusted thymus weights for male and female dogs combined at the mid and high doses were increased to 109.3 and 107.8% of the control (20.5[A] g), respectively.

Thyroid: Adjusted thyroid weights for female dogs at the low, mid, and high doses were increased to 105.4, 112.9, and 126.9% of the control (0.93[A] g), respectively.

Uterus: Absolute and adjusted uterus weights for female treatment groups were increased to 107.5-128.4% and 117.5-133.3% of the control (0.67 and 0.63[A] g), respectively, although, dose-response relationships were not evident.

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)

Histopathology findings were observed in lung, heart, kidneys, adrenals, and duodenum of dogs in the high dose group at the end of the 4-week treatment

period as shown in the table below. Given the low incidence of most of these findings (i.e., 1 of 6 dogs), relationships to treatment were unclear. Recovery of these lesions was difficult to assess as histopathological examination of tissues from recovery animals was limited to macroscopic findings, which were only apparent in the lungs, heart, and/or jejunum.

Findings of exudate containing foamy macrophages in bronchioles for 2 dogs as well prominent BALT for 1 dog may be indications of local toxicity related to the inhalation of magnesium stearate. These may be nonspecific findings associated with inhalation of dust. These findings were not evident at the end of the 4-week recovery period. For poorly soluble particles (i.e., carbon black, coal, diesel, soot, talc, and titanium dioxide) that are inhaled into the lung, an overload phenomenon has been described in which excessive levels of dust lead to a failure of alveolar macrophage-mediated clearance of these particles induced by a volumetric overload (Toxicology and Applied Pharmacology 145: 10-22, 1997; Regulatory Toxicology and Pharmacology 27: 123-135, 1995; Toxicology and Applied Pharmacology 113: 1-12, 1992; Fundamental and Applied Toxicology 10: 369-384, 1988). Normal linear clearance kinetics became nonlinear. Magnesium stearate is not soluble in water and may share some similarities to these poorly soluble particulates. General characteristics of pulmonary responses during overload can include stasis or slowing of alveolar macrophage-mediated clearance of these particles, significant and diverse accumulation of particle-laden macrophages within the pulmonary alveoli, increased translocation and accumulation of particles in the interstitium of the lung and in the lymph nodes of the thoracic cavity, and various pathological consequences (i.e., chronic inflammation, alveolitis, granulomatous lung disease, and lung tumors). Observations of exudate with foamy macrophages and prominent BALT observed at the high dose may be consequences of an overload phenomenon associated with high concentrations of dust and insoluble magnesium stearate particles.

The findings in the heart of blood filled cystic spaces on heart valves are considered to be spontaneous background findings given their occurrence in 1 control male at the end of the 4-week recovery period. Further, the background incidence of this finding is 0.4% (4/1000; Handbook of Toxicology 2nd Edition, CRC Press, 2002, Page 727).

Histopathology findings[a] at the end of the 4-week treatment period.

| Organ/Tissue | Sex | Control | Low Dose | Mid Dose | High Dose |
|---|---|---|---|---|---|
| **Lungs** | | | | | |
| -exudate containing foamy macrophages in bronchioles, minimal | M | 0/3 | 0/3 | 0/3 | 1/3 |
| | F | 0/3 | 0/3 | 0/3 | 1/3 |
| -prominent bronchial associated lymphoid tissue (BALT) | M | 0/3 | 0/3 | 0/3 | 1/3 |
| | F | 0/3 | 0/3 | 0/3 | 0/3 |
| **Heart** | | | | | |
| -blood filled cystic spaces on | M | 0/3 | 0/3 | 0/3 | 1/3 |

| | | | | | |
|---|---|---|---|---|---|
| heart valve | F | 0/3 | 0/3 | 0/3 | 0/3 |
| **Kidneys** | | | | | |
| -focus of basophilic cortical tubules | M | 0/3 | 0/3 | 0/3 | 0/3 |
| | F | 0/3 | 0/3 | 0/3 | 1/3 |
| **Adrenals** | | | | | |
| -vacuolation of cells in zona glomerulosa (minimal) | M | 0/3 | 0/3 | 0/3 | 0/3 |
| | F | 0/3 | 0/3 | 0/3 | 1/3 |
| **Duodenum** | | | | | |
| -congestion and hemorrhage in mucosa of bile duct openings | M | 0/3 | 0/3 | 0/3 | 0/3 |
| | F | 0/3 | 0/3 | 0/3 | 1/3 |

a. Light microscopic examination was conduced on formalin-fixed, hematoxylin and eosin stained 4 µm thick sections of tissues. All tissues were examined for dogs in Groups 1, 2, 3, and 4 at the end of the 4-week treatment period. Macroscopically abnormal tissues were examined for dogs in Groups 1 and 4 at the end of the 4-week recovery period. For lung, sections of the left and right apical, cardiac and diaphragmatic lobes including bronchus/bronchioles and surrounding tissue and sections containing peripheral lung parenchyma were examined.

Toxicokinetics: Not performed.

**Study title: Response to Division Questions Regarding the 13-week Bridging Toxicology Study with Dogs (Originally submitted under IND 60,254).**

**Study no:** Reference Number 992022
**Conducting laboratory and location:** [redacted]

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In a FAX communication to the sponsor on March 21, 2001, the sponsor was requested to address the three questions generated from the review of the 13-week inhalation toxicity study in dogs (see Review #02 dated April 2, 2001). The sponsor's response in Amendment #014 dated April 2, 2001 are listed below.

Question 1:

[redacted]

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Question 2:

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Question 3:
The ratio refers to a weight to weight basis.

**Evaluation:**
The sponsor's responses in Questions 1, 2, and 3 appear adequate and resolve outstanding issues from the review of the 13-week inhalation toxicology study with dogs.

**Histopathology inventory (optional)**

| Study | Magnesium stearate/ 4-week exposure |
|---|---|
| Species | Dogs |
| Adrenals | X* |
| Aorta | X |
| Bone Marrow smear | |
| Bone (femur) | X |
| Brain | X* |
| Cecum | X |
| Cervix | |
| Colon | X |
| Duodenum | X |
| Epididymis | X |
| Esophagus | X |
| Eye | X |
| Fallopian tube | |
| Gall bladder | X |
| Gross lesions | X |
| Harderian gland | |
| Heart | X* |
| Ileum | X |
| Injection site | |
| Jejunum | X |
| Kidneys | X* |

| | |
|---|---|
| Lachrymal gland | X |
| Larynx | X |
| Liver | X* |
| Lungs | X* |
| Lymph nodes, cervical | X |
| Lymph nodes mandibular | |
| Lymph nodes, mesenteric | X |
| Lymph nodes, tracheobronchial | X |
| Mammary Gland | X |
| Nasal cavity | X |
| Optic nerves | X |
| Ovaries | X* |
| Pancreas | X |
| Parathyroid | X |
| Peripheral nerve | |
| Pharynx | X |
| Pituitary | X* |
| Prostate | X* |
| Rectum | X |
| Salivary gland (submandibular) | X |
| Sciatic nerve | X |
| Seminal vesicles | |
| Skeletal muscle | X |
| Skin | X |
| Spinal cord | X |
| Spleen | X* |
| Sternum | |
| Stomach | X |
| Testes | X* |
| Thymus | X* |
| Thyroid | X* |
| Tongue | X |
| Trachea | X |
| Urinary bladder | X |
| Uterus | X |
| Vagina | X |
| Zymbal gland | |

X, histopathology performed
*, organ weight obtained

### 3.4.4. Genetic toxicology

For reviews of genetic toxicology studies conducted with formoterol fumarate, refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

### 3.4.5. Carcinogenicity

For reviews of carcinogenicity studies conducted with formoterol fumarate, refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

### 3.4.6. Reproductive and developmental toxicology

For reviews of reproductive and developmental toxicology studies conducted with formoterol fumarate, refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

### 3.4.7 Local tolerance

For reviews of local tolerance studies conducted with formoterol fumarate, refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

### 3.4.8 Special toxicology studies

For reviews of special toxicology studies conducted with formoterol fumarate, refer to NDA 20-831 (Novartis, Foradil® Aerolizer™).

## 3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Formoterol fumarate (Foradil® Aerolizer) has been approved for the treatment of asthma (NDA 20-831) and chronic obstructive pulmonary disease (NDA 21-279). The new formulation in the present application differs from the formulation in NDAs 20-831 and 21-279. The new formulation uses two excipients, lactose and magnesium stearate, while the older formulation used lactose only. Lactose is a well-known excipient for inhalation drug products and its safety has been established. Magnesium stearate has been used extensively as an excipient for oral drug products, but never as an excipient for inhalation drug products. Thus, inhalation use of magnesium stearate is a significant safety concern in the evaluation of the dry powder inhaler (DPI). The second significant safety concern relates to potential changes of product performance (i.e., increased delivery of active ingredient).

From a preclinical standpoint, to address concerns regarding the inhalation use of magnesium stearate and potential changes of produce performance, the sponsor has conducted 1- and 6-month inhalation toxicology studies with magnesium stearate in rats, a 1-month inhalation toxicology study with magnesium stearate in dogs, and a 3-month bridging inhalation toxicity study in dogs to compare the new formulation (with magnesium stearate and lactose) and old formulation (with lactose).

Magnesium stearate is a direct food substance affirmed as generally recognized as safe (GRAS, 21 CFR 184.1440). Magnesium stearate can be used in food with no limitation other than current good manufacturing practice. Magnesium stearate is also used as a lubricant and release agent (21 CFR 170.3(o)(18)), a nutrient supplement (21 CFR 170.3(o)(20)) and a processing aid (21 CFR 170.3(o)(24)). Based upon the GRAS status of magnesium stearate in food, there are no significant concerns regarding systemic toxic effects. Evaluation of inhalation toxicology studies conducted with magnesium stearate

will be primarily directed toward identification of potential local toxic effects in the pulmonary system. The inhaled dose of magnesium stearate is more than — fold less than the oral dose. b(4)

Magnesium stearate is a commonly used inactive ingredient in drug products. Treatment with Zyflo® (Zileuton; 600 mg/tablet x 4 tablet/day) includes the inactive ingredient, magnesium stearate, at a dose of —mg/day ( —mg tablet x 4 tablets/day). This dose of magnesium stearate is approximately — times the proposed dose of magnesium stearate used with Foradil® Certihaler. b(4)

In the initial submission of IND 60,254, the sponsor submitted results of 1- and 6-month inhalation toxicity studies with magnesium stearate in rats. In the 1-month study with rats that received a deposited dose of 26 µg/kg/day, there was no evidence of local toxic effects. For the 6-month inhalation toxicology study with rats that received that received deposited doses of 0.9, 20, 60, and 180 µg/kg/day for 6 months, there was no evidence of treatment-related local toxic effects in the pulmonary system. The NOAEL of 180 µg/kg/day in rats is — and — times proposed doses for children ( µg/kg/day) and adults ( µg/kg/day), respectively. b(4)

In a letter from the Division dated August 17, 2000, the sponsor was asked to justify their selection of the rat as the most appropriate species for the 6-month inhalation toxicity study. In the letter, it was stated that "Generally, species selection is based on short-term studies conducted in rodent and nonrodent species."

In Amendment #022 dated August 28, 2001, the sponsor provided a study report for a 4-week inhalation toxicology study with magnesium stearate in dogs, which was sponsored by and completed in 1994. For dogs that received magnesium stearate at deposited doses of 0.02, 0.3, and 6.3 mg/kg/day, there were findings in the lungs at the high dose that consisted of exudate containing foamy macrophages in bronchioles for 2 of 6 dogs as well prominent bronchial-associated lymphoid tissue for 1 of 6 dogs. b(4)

These findings in the lung may be indications of local toxicity related to the inhalation of magnesium stearate, although, their low incidences place some doubts on the treatment relationships of these findings. Inflammation in the lungs of beagle dogs is a very common finding and occurs in a variety of forms that include perivasculitis, peribronchiolitis, pleuritis, subpleural fibrosis, endobronchiolitis, interstitial pneumonia, bronchopneumonia, and various granulomas (Handbook of Toxicology, 2nd Edition, Page 730). It is unclear if these findings encompass the observations of exudate containing foamy macrophages in bronchioles and prominent BALT in the present study.

It is possible that these findings at the high dose in the present study may be of a nonspecific nature associated with inhalation of high concentrations of

dust. It should be emphasized that these findings were observed at low incidences (i.e., 2 of 6 and 1 of 6) and not generalized to the entire group. These findings in dogs occurred at a dose that is —— and —— times proposed doses for children and adults, respectively. This phenomenon was not evident with the mid and low doses. Further, this phenomenon, which has been more definitely described in rats, was not observed in the chronic rodent study. The NOEL of 0.3 mg/kg/day in dogs is —— and —— times proposed doses for children and adults, respectively. Thus, these findings at the high dose would appear to have little relevance to the proposed clinical dose. b(4)

Comparison of the 1 month inhalation toxicity studies with magnesium stearate in rats and dogs suggest that it was possible to administer higher doses to dogs that rats. However, for both rats and dogs, magnesium stearate was delivered at deposited doses ranging from 1 to 2 orders of magnitude greater than the proposed clinical dose with no adverse findings. Thus, the 6-month inhalation toxicity study with magnesium stearate in rats would appear to be acceptable.

Based upon the 6-month inhalation toxicology with magnesium stearate in rats as well as the GRAS status of magnesium stearate in foods and the large ratio between safe oral doses and the proposed inhaled dose, the use of magnesium stearate as an inactive ingredient in the proposed drug product appears safe.

The sponsor conducted a 13-week bridging study with beagle dogs using the inhalation route to assess differences in the toxicity of a new formulation of formoterol with excipients, lactose and magnesium stearate, as compared to the older formulation of formoterol with lactose only. Toxicity profiles of the new and old formulations were comparable with particular reference to the heart in terms of heart rate, ECG findings, and histopathology. Plasma and urinary pharmacokinetic data indicated that systemic exposure to formoterol was increased by approximately 1.5 to 3.0-fold with the new formulation as compared to the old formulation. Based upon inhalation toxicology studies conducted with the formoterol dry powder in rats for periods ranging from 1 to 12 months (see table below), adequate safety margins appear to be present in adults based upon deposited dose. Safety margins for children that are treated for periods ≥3 months are low, but considered acceptable in this particular case. The dose-limiting finding in the 6/12-month inhalation toxicology study with rats was a degeneration of the seminiferous tubules in the testes. Safety margins were never established based upon studies conducted with dogs due to dose-limiting cardiovascular effects (i.e., increased heart rate, ECG findings, and myocardial fibrosis).

Safety margins for the clinical dose of formoterol fumarate MDDPI in adults and children based upon studies with the dry powder formulation in rats and dogs.

| Species | Study Duration | Doses (Deposited Dose[a]) µg/kg/day | NOAEL (Deposited Dose[a]) µg/kg/day | Safety margins for the clinical dose of formoterol MDDPI | |
|---|---|---|---|---|---|
| | | | | 20 µg/50kg = 0.4 | 20 µg/16kg = 1.25 |
| Rat | 28-days Dry powder | 16, 50, & 115.3 | 115.3 | 288 | 92 |
| | 3-months Dry powder | M: 0.25, 0.8, & 2.6 F: 0.4, 1.2, & 3.9 | 2.6/3.9 | 6.5/9.8 | 2/3.1 |
| | 6/12-months Dry powder | 3, 12, & 40 | 3 | 7.5 | 2.4 |
| Dog | 4-Weeks Dry powder | 0.6, 2.8, & 11 | None[b] | - | - |

a. Deposited doses were determined by multiplying the inhaled dose by 0.10 for rats and 0.25 for dogs.
b. A NOAEL was not established in the 4-week inhalation toxicology study with formoterol in dogs based upon findings of increased heart rate and myocardial fibrosis at all doses. The 6/12-month inhalation toxicology study with dogs was considered to be inconclusive and therefore, insufficient for calculation of safety margins.

**Unresolved toxicology issues (if any):** None.

**Recommendations:** From a preclinical standpoint, approval of the application is recommended.

**Suggested labeling:**

b(4)

3 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

**Signatures (optional):**

**Reviewer signature:** _____
Timothy W. Robison, Ph.D.

**Supervisor signature:** _____
Joseph Sun, Ph.D.

**Concurrence: Yes ___ No ___**

**cc: list:**
NDA 21-592 Division File, HFD-570
IND 60,254 Division File, HFD-570
GreenA, HFD-570
SunC, HFD-570
RobisonT, HFD-570

## *3.7.* APPENDIX/ATTACHMENTS

APPENDIX 1: IND 60,254 Review #01 dated June 7, 2000
1- and 6-month inhalation toxicology studies with magnesium stearate in rats.

APPENDIX 2: IND 60,254 Review #02 dated April 2, 2001
13-week inhalation bridging toxicology study in dogs.

APPENDIX 1: IND 60,254 Review #01 dated June 7, 2000
1- and 6-month inhalation toxicology studies with magnesium stearate in rats.

**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**
**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

**REVIEW INFORMATION:**

| | |
|---|---|
| **Review No.:** | 1 |
| **Date of Completion:** | June 7, 2000 |
| **Reviewer Name:** | Luqi Pei, Ph.D. |
| **Key Words:** | Formoterol, magnesium stearate, inhalation |
| **Information to be Conveyed to Sponsor:** | Yes x No |

**APPLICATION INFORMATION:**

| | | |
|---|---|---|
| **IND Application No:** | | IND 60,254 |
| **Serial No., Content and Date of Submission:** | | 000, Original submission, April 27, 2000 |
| **Sponsor:** | | Novartis Pharmaceutical Corporation, East Hanover, NJ |
| **Drug Name:** | *Generic Name:* | Formoterol fumarate dihydrate |
| | *Code Name:* | CGP 25827 A |
| | *Brand Name:* | Foradil™ (Formoterol fumarate multi-dose DPI) |
| | *Chemical Name:* | (±)-2-hydroxy-5-[1(1RS)-hydroxy-2-[[(1RS)2-(4-ethoxyphenyl)-1-ethylethyl]amino]ethyl]-phenyl]formamide, (E)-2-butanedionate (2:1) (salt) |
| | *Molecular Weight and Formula:* | $C_{42}H_{52}N_4O_{12}\cdot 2H_2O$, MW= 804 (free base) |
| | *CAS No.:* | 43229-80-7 |
| **Class:** | | Beta 2 adrenergic bronchodilator |

**Review Summary:**

This review evaluates preclinically the safety of a proposed clinical study protocol for a formoterol dry powder inhaler (DPI). The protocol proposes to study the time of onset of formoterol action in 16 asthmatic patients. The proposed formoterol doses are 10 or 20 μg per treatment. Formulation of the DPI consists of formoterol, lactose and magnesium stearate. The application refers to an NDA application (NDA 20-831) for the preclinical data to support the safety of formoterol and lactose. (The Division currently considers NDA 20-831 approvable.) Magnesium stearate, as an inactive ingredient or excipient, has been used in a variety of approved formulations, but not in any inhalation drug products. To qualify the inhalation use of magnesium stearate, the sponsor conducted two inhalation toxicity studies of the compound in rats. These studies, with the exposure duration of up to 6 months, showed that the 6-month NOAEL of magnesium stearate by inhalation was 180 μg/kg/day, the highest dose tested. This NOAEL value in rats is approximately — fold greater than the expected clinical dose in humans. These preclinical data support the safe inhalation use of magnesium stearate in the protocol. Overall, the review concludes that the available data support the safety of the formoterol DPI. Thus, the review recommends from the preclinical viewpoint that the protocol be allowed to proceed. b(4)

**ADDITIONAL INFORMATION:**

| | |
|---|---|
| **Related INDs and NDAs:** | NDA-20-831 and IND 47,013 |
| **Related DMFs:** | Not indicated |
| **Proposed Clinical Use:** | Asthma |
| **Route of Administration:** | Oral inhalation |
| **Previous Clinical Experience:** | Pivotal phase 3 trials of Foradil DPI (formoterol + lactose) have been completed. NDA 20-831 is approvable. |

**Proposed Clinical Formulation:**

| Ingredients | Amount (mg)/actuation | | b(4) |
|---|---|---|---|
| Formoterol fumarate | [redacted] | [redacted] | |
| Lactose monohydrate | [redacted] | [redacted] | |
| Magnesium stearate | | | |

**Documents Submitted and Included in This Review:**

| Study # | Description | Vol/page | b(4) |
|---|---|---|---|
| 731575 | 1-mo. inhalation toxicity study with magnesium stearate in rats | 3/8-39 | |
| 724353 | 6-mo. inhalation toxicity study with magnesium stearate and lactose in rats | 4/8-260 | |
| 708401 | Use of magnesium stearate excipient in lactose formulations | 3/8-15 | |

**Proposed Protocol:** A randomized, double-blind, placebo controlled, four-period cross-over study to evaluate the onset of action of 10 and 20 µg of formoterol fumarate delivered via the MDDPI compared to 180 µg of albuterol (salbutemol) in subjects with persistent asthma (Protocol study No. CFOR258F0608).

**Disclaimer:** *Note some material may be taken directly from the sponsor's submission*

## INTRODUCTION

Novartis proposes to study the onset of formoterol action in asthmatic patients using a new formulation. The formulation consists of formoterol, lactose and magnesium stearate. Functions of these components are active ingredient, [redacted] respectively. The level of each component can be found in the proposed clinical formulation section. b(4)

Sufficient preclinical and clinical experience with formoterol is available. The sponsor refers to NDA 20-831, Foradil Aerolizer, to support the safety of their protocol because both this IND application and NDA 20-831 use the same drug for the same indication - asthma. The Division has twice considered NDA 20-831 approvable because of deficiencies in manufacturing and controls processes. No outstanding clinical or preclinical issues remain to prevent the approval of the NDA.

Because of the history of the Foradil application (NDA 20-831), this submission contained no

preclinical data for formoterol. The submission made a reference to NDA 20-831 for all of pharmacology and toxicology data for formoterol and lactose because NDA 20-831 has fully evaluated the toxicology of formoterol. Detailed reviews and evaluation can be found in various pharmacology and toxicology reviews of that application.

However, the new formulation differs from the formulation in NDA 20-831. The new formulation uses two excipients: lactose and magnesium stearate while the old formulation uses lactose only. Lactose is a well-known excipient for inhalation drug products and its safety has been established. Magnesium stearate, on the other hand, has never been used as an excipient for inhalation drug products before. Thus, inhalation use of magnesium stearate becomes a safety concern in the safety evaluation of the DPI. This concern was conveyed to the sponsor in a pre-IND meeting held on June 30, 1999.

In the pre-IND meeting, the sponsor and the Division agreed the following:

1. A 6-month inhalation toxicity study is needed to support the chronic inhalation use of magnesium stearate.
2. A 3-month bridging inhalation toxicity study is needed to compare the new formulation (with magnesium stearate and lactose) and old formulation (with lactose). This study must be completed before the initiation of phase 3 clinical trials.
3. The above studies should be conducted in the most appropriate species and Novartis will determine which species is more appropriate.

Novartis has conducted and submitted two inhalation toxicity studies with the exposure duration of one- and six-months in rats to evaluate the toxic effect of magnesium stearate on the respiratory system. This review is generated to evaluate these two studies and the safety of the proposed protocol.

## REVIEW

**General Toxicology:**

1. **One-month Inhalation Toxicity Study with Magnesium Stearate in Rats. Projects No, 731575. Vol. 3, page 8-39.**

*Testing Laboratory:* [redacted]

b(4)

| | |
|---|---|
| *Study Number:* | [redacted] Project No. 731575 |
| *GLP Statement* | Yes |
| *Study Date:* | 4/21/99 –6/29/99; Final Report date: 9/15/1999 |
| *Lot Number:* | 96114/2 (expiration date 10/16/99) |
| *End Point:* | Toxicity of inhaled Mg stearate on respiratory system |

**Method**

Wistar rats (5 rats/sex/dose, 7 –11 weeks of age) were exposed by nose-only inhalation to 0 or 26 µg/kg/day (pulmonary deposition[1]) magnesium stearate for 30 days. The control group received room air only. The duration of exposure was 1 hour/day for both groups. The mean aerosol concentration for magnesium stearate was 8.1±2 µg/l air. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) for the treatment group were [redacted] µm ± [redacted] b(4)

The following parameters were monitored during the study:

| | |
|---|---|
| *Clinical Signs:* | Weekly |
| *Body Weight:* | Weekly |
| *Food Consumption:* | Weekly |
| *Ophthalmology:* | Pre-exposure and Week 4 |
| *Clinical Pathology:* | Hematology, blood chemistry, and urinalysis examinations on day 30 of the exposure |
| *Pathology:* | Time of sacrifice |
| *Organ Weights:* | Adrenals, brain, heart, kidneys, liver, lungs, spleen, testes/ovaries, thymus, thyroids |
| *Necropsy:* | All animals |
| *Histopathology:* | Respiratory tract only: nasal cavity, nasopharynx, larynx, lungs, lymph-nodes, trachea and bronchi. |

**Results**

*Clinical signs:* No deaths or treatment-related clinical signs were observed.
*Body Weights*: No treatment-related effects were observed.
*Food Consumption:* No treatment-related effects were observed.
*Ophthalmology:* No treatment-related effects were observed.
*Hematology:* No treatment-related effects were observed.
*Clinical Chemistry:* No treatment-related effects were observed.
*Organ Weight:* No treatment-related effects were observed.
*Histopathology:* No treatment-related effects were observed.

*Key Study Observations:* Administration of magnesium stearate to Wistar rats at inhalation doses of 26 µg/kg/day did not result in any treatment-related findings. The no-observed-adverse-effect-level (NOAEL) for magnesium stearate can be tentatively identified as 26 µg/kg/day in rats, as the study had a relatively small sample size.

1. The study report cites a magnesium stearate dose of 258 µg/kg/day. This is an expected amount in the inhaled air (8.1 µg/l x 0.134 l/min x 60 min ÷ 0.25 kg = 258 µg/kg/day). The Division uses the expected pulmonary dose for the safety evaluation of inhalation drugs indicated for asthma. The pulmonary dose of magnesium stearate in this study would be 26 µg/kg/day, using a pulmonary deposition factor of 0.1 in rats.

**1. Six-month Inhalation Toxicity Study with Magnesium Stearate in Rats. — Projects No, 724353. Vol. 4, page 8-260.**

*Testing Laboratory:* [redacted] b(4)

*Study Number:* — Project No. 724353
*GLP Statement* Yes
*Study Date:* 4/21/99-11/3/99; Final Report date: 3/10/2000
*Lot Number:* 96114/2 and S9D050 (expiration date: 3/31/2000)
*End Point:* Toxicity of inhaled Mg stearate on respiratory system

**Method**

Wistar rats (10 rats/sex/dose, 7 – 11 weeks of age) were exposed by nose-only inhalation to magnesium stearate or magnesium stearate in lactose (1%, w/w) for 26 weeks. Magnesium stearate dose levels were 0, 0.9, 20, 60 and 180 µg/kg/day (pulmonary deposition). The 0.9 µg/kg/day group was also exposed to 90 µg/kg/day of lactose monohydrate. The control group of rats received room air only. The duration of exposure was 1 hour/day for all groups. Table 1 presents the estimates of magnesium stearate dose levels in the study.

Table 1. Estimates Of Magnesium Stearate Dose Levels in Rats.

| Group | Aerosol Particles | | Mg stearate | Estimated exposure (µg/kg/day) | |
|---|---|---|---|---|---|
| | MMAD | GSD | (µg/L air) | Total body | Pulmonary |
| 1 | [redacted] | | 0 | 0 | 0 |
| 2 | | | 0.293 | 9.3 | 0.9 |
| 3 | | | 6.31 | 200 | 20 |
| 4 | | | 18.94 | 600 | 60 |
| 5 | | | 56.81 | 1800 | 180 |

b(4)

The report gave the following as the rationale for the dose selection. [redacted]

— between rats and humans. According to the current division practice that only pulmonary dose should be used as the actual exposure in rats, the low dose is only one-tenth of the expected clinical dose. Such a low dose is meaningless for the purpose of safety evaluation. Nonetheless, the selection of the high dose is reasonable.

2 . The sponsor calculated their human dose as the following: [redacted] b(4)

The following parameters were monitored during the study:

| | |
|---|---|
| *Clinical Signs:* | Daily |
| *Clinical exams:* | Weekly |
| *Body Weight:* | Weekly |
| *Food Consumption:* | Weekly |
| *Ophthalmology:* | Pre-exposure and Week 26 |
| *Clinical Pathology:* | Hematology, blood chemistry, and urinalysis examinations in weeks 6 and 26 of the exposure |
| *Pathology:* | Time of sacrifice |
| *Organ Weights:* | Adrenals, brain, heart, kidneys, liver, lungs, spleen, testes/ovaries, thymus, thyroids |
| *Necropsy:* | All animals |
| *Histopathology:* | Respiratory tract of animals at all doses: nasal cavity, nasopharynx, larynx, lungs, lymph-nodes, trachea and bronchi.<br>All organs/tissues from animals that died spontaneously.<br>All organs/tissues with gross lesions. |

**Results**

*Clinical signs:* No treatment-related clinical signs were observed. One mid-dose male (rat No. 34) died of purulent prostatitis on day 179. This death is not considered treatment-related.
*Body Weights*: No treatment-related effects were observed.
*Food Consumption:* No treatment-related effects were observed.
*Ophthalmology:* No treatment-related effects were observed.
*Hematology:* No treatment-related effects were observed.
*Clinical Chemistry:* No treatment-related effects were observed.
*Organ Weight:* No treatment-related effects were observed.
*Histopathology:* No treatment-related effects were observed.

*Key Study Observations:* Administration of magnesium stearate to Wistar rats at inhalation doses of up to 180 µg/kg/day did not result in any treatment related findings. The no-observed-adverse-effect-level (NOAEL) for magnesium stearate can be identified as 180 µg/kg/day in rats.

**Summary of Toxicity Studies**

The effect of magnesium stearate on the respiratory system was evaluated in two inhalation studies in rats. Their durations of exposure were 1- and 6-month, respectively. The doses (pulmonary deposition) were 26 µg/kg/day for the 1-month study and 1, 20, 60 and 180 for the 6-month study. Neither study revealed any treatment-related abnormalities in the respiratory system. The 6-month NOAEL value for magnesium stearate in rats was 180 µg/kg/day with the inhalation route of exposure.

**3. Use of Magnesium Stearate Excipient in Lactose Formulations, —project No. 708401, page 8-15.**

This is a literature review conducted by — in 1998. — is the contract laboratory that performed the above two inhalation-toxicity studies of magnesium stearate in rats. The — review contains no significant information for the safety evaluation of inhalation magnesium stearate, but the following is note-worthy: b(4)

The American Conference of Governmental Industrial Hygienists (ACGIH) has a TLV-TWA of 10 mg/m$^3$ for magnesium stearate. The effect of magnesium stearate on the respiratory system after long-term inhalation exposure is unknown. The laboratory has limited experience with the mixture of magnesium stearate and lactose in repeat-dose inhalation toxicity studies, but it cannot provide this formation to the sponsor due to confidentiality. Overall, the review states "Short-term bridging inhalation toxicity studies in rodents, generally required by regulatory authorities, are warranted...."

## OVERALL SUMMARY AND EVALUATION

This application, sponsored by Novartis, proposes to study the onset of formoterol action in asthmatic patients using a dry powder inhaler of a new formulation. This submission contained a protocol (Protocol No. CFOR258F0608) entitled "A randomized, double-blind, placebo controlled, four-period cross-over study to evaluate the onset of 10 and 20 µg of formoterol fumarate delivered via the MDDPI compared to 180 µg of albuterol (salbutemol) in subjects with persistent asthma." The protocol plans a total enrollment of 16 patients. Formulation of the DPI consists of formoterol, lactose and magnesium stearate. The review evaluates the safety of this protocol according to the components of the device.

*Formoterol*

Formoterol, the active ingredient, is a long acting beta 2 agonist that has good bronchodilatory effect. The drug has been approved for the indication of asthma in numerous countries. In the US, several sponsors are developing the drug for the same indication. In fact, the agency has determined that Novartis formoterol product, Foradil Aerolizer (NDA 20-831), is approvable. Foradil Aerolizer is a formoterol dry powder inhaler that consists of formoterol and lactose.

Sufficient preclinical and clinical data is available to support the safety of formoterol in the new protocol. These data can be found in the Foradil application (NDA 20-831) that the sponsor has referred to, and have been reviewed by the Division. As a result, this submission contains no data for formoterol because toxicology of the drug has been thoroughly evaluated in the referenced NDA.

**Lactose**

Lactose is an excipient used both in the new and old formulations. The Division has determined that the safety of lactose as an excipient in inhalation drug products is established by available clinical and preclinical data.

**Magnesium Stearate**

Magnesium stearate is a [redacted]' added in the formulation. Magnesium stearate is a well-known excipient for oral drug products. The CDER Inactive Ingredient Guide (1996) indicates that over 2,000 drug products contain magnesium stearate. However, magnesium stearate has not been used as an excipient for inhalation drug products. Thus, inhalation use of magnesium stearate becomes a safety concern in the safety evaluation of the DPI. This concern was conveyed to the sponsor in a pre-IND meeting held on June 30, 1999. Novartis was asked to conduct inhalation toxicity studies with treatment duration of up to 6 months to evaluate the effect of magnesium stearate on the respiratory tract in animals. b(4)

Novartis has conducted and submitted two inhalation toxicity studies with exposure durations of one- and six-months in rats to evaluate the toxic effect of magnesium stearate on the respiratory system. These studies showed that magnesium stearate treatment by inhalation for 6 months at doses of up to 180 µg/kg/day, the highest dose tested, did not cause any treatment-related abnormalities in the respiratory system in rats. This dose, considered a 6-month NOAEL value in rats, is approximately [redacted]-fold greater than the expected exposure in humans ([redacted] µg/kg/day). It is concluded that there is sufficient margin of safety to support the safety of magnesium stearate in the proposed protocol. b(4)

**Recommendation**

From the preclinical viewpoint, this protocol is safe to proceed.

**Comment to Sponsor:**

Justify your selection of the rat as the most appropriate species for the 6-month inhalation toxicity study. Generally, species selection is based on short-term studies conducted in rodent and non-rodent species.

Luqi Pei, D.V.M., Ph.D.
Pharmacologist/Toxicologist

Robin Huff, Ph.D.
Pharm/Tox Team Leader

Ori: IND 60,254/HFD-570/Division File
HFD-570/Drs. Pei /Huff/Anthracite /Bertha/ Jani

APPENDIX 2: IND 60,254 Review #02 dated April 2, 2001
13-week inhalation bridging toxicology study in dogs.

APPEARS THIS WAY ON ORIGINAL

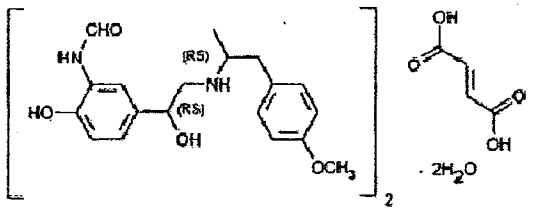
# PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

**IND number:** 60,254
**Review number:** #002
**Sequence number/date/type of submission:**
Amendment #006 dated November 8, 2000
Amendment #007 dated November 29, 2000
Amendment #012 dated January 17, 2001
**Information to sponsor: Yes (X) No ( )**
**Sponsor and/or agent:** Novartis Pharmaceutical Corporation
59 Route 10
East Hanover, NJ 07936-1080
**Manufacturer for drug substance:** Skye Pharma

**Reviewer name:** Timothy W. Robison, Ph.D.
**Division name:** Pulmonary and Allergy Drug Products
**HFD #:** 570
**Review completion date:** April 2, 2001

**Drug:**

**Trade name:** Foradil® Multidose Dry Powder Inhaler
**Generic name (list alphabetically):** Formoterol fumarate dihydrate
**Code name:**
**Chemical name:** (±)-2-hydroxy-5-[1(1RS)-hydroxy-2-[[(1RS)2-(4-ethoxyphenyl)-1-ethylethyl]amino]ethyl]-phenyl]formamide, (E)-2-butanedionate (2:1) (salt)
**CAS registry number:** 43229-80-7
**Mole file number:**
**Molecular formula/molecular weight:** $C_{42}H_{52}N_4O_{12}.2H_2O$; MW = 804 (free base)
**Structure:**




**Relevant INDs/NDAs/DMFs:** IND 34,342 (Novartis Pharmaceutical Corporation, formerly Ciba-Geigy)
IND 47,013 (Novartis Pharmaceutical Corporation)
NDA 20-831 (Novartis Pharmaceutical Corporation)

**Drug class:** $\beta_2$-Adrenergic Bronchodilator

**Indication:** Asthma

**Clinical formulation:** The formulation consists of [redacted] drug substance, magnesium stearate, and lactose ([redacted]). The magnesium stearate is used to [redacted]. The formulation is intended for use in a multi-dose dry powder inhaler that contains 60 doses (puffs) for inhalation. b(4)

**One 8.5 µg emitted dose contains:**

| Ingredient | Theoretical amount (mg) | Function |
|---|---|---|
| Formoterol fumarate dihydrate | 0.0085* | Drug Substance |
| Lactose monohydrate ([redacted]) | [redacted] | [redacted] |
| Magnesium Stearate | [redacted] | [redacted] |

b(4)

**Route of administration:** Oral inhalation

**Proposed clinical protocol:** An End of Phase 2 Meeting was held with the sponsor on January 29, 2001. The sponsor plans to initiate Phase 3 clinical trials within the near future. The sponsor has proposed that the Foradil 8.5 µg emitted dose (10 µg metered dose) in the MDDPI device is the appropriate dose for use in the Phase 3 program. The amount of magnesium stearate that will be administered is estimated to be [redacted] µg/actuation. If a maximum number of 4 puffs were assumed, the maximum daily dose of magnesium stearate would be [redacted] µg. b(4)

**Previous clinical experience:** The sponsor has conducted two Phase 2 dose finding trials, one in adults and adolescents (Study 601) and one in children, between 5 and 12 years of age, (Study 602). The objective of these studies was to determine an optimal effective dose of formoterol powder delivered from the multi-dose dry powder inhaler (MDDPI). The effects of four doses of formoterol (5, 10, 15, and 30 µg metered dose b.i.d.) delivered from the MDDPI were assessed for bronchodilation response.

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

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ON ORIGINAL

## OVERALL SUMMARY AND EVALUATION:

**Introduction:**

The sponsor conducted a 13-week bridging study with beagle dogs using the inhalation route to assess differences in the toxicity of a new formulation of formoterol with excipients, lactose and magnesium stearate, as compared to the older formulation of formoterol with lactose only. Deposited formoterol doses of the new formulation for the low, mid, and high dose groups were 0.5, 1.7, and 5 µg/kg/day, respectively. The deposited dose for the old formulation was 3.3 µg/kg/day. There were no differences in the toxicity profiles between the new and old formulations of formoterol. The deposited formoterol dose of 0.5 µg/kg/day for the new formulation could be considered the NOAEL given the sporadic nature of electrocardiographic changes and no histopathological findings at this dose. The dose of magnesium stearate at the NOAEL was 1 µg/kg/day. Control animals received a deposited dose of magnesium stearate at 9.7 µg/kg/day with no evident adverse findings. Electrocardiographic examinations found that heart rate was increased for male and female treatment groups receiving the new formulation (low, mid, and high doses) and old formulation. Decreased Q-T and P-Q intervals as well as increased P wave amplitudes were also observed and probably associated with increased heart rates. Incidences of altered T wave polarity were increased in a dose-related manner, and were particularly predominant for the new formulation at the high dose and the old formulation. Increased heart rate may be attributed to either stimulation of cardiac $\beta_1$-receptors or a compensatory response to $\beta_2$-receptor-mediated peripheral vasodilation. There were no apparent treatment-related target organs of toxicity, although, papillary muscle fibrosis of the heart was observed for 1 male dog that received the new formulation at the mid dose. Plasma AUC values for formoterol in male and female dogs that received the new formulation at the high dose were, in general, approximately 1.5 times the values observed in male and female dogs that received the old formulation, possibly reflecting the same proportional difference in deposited dose. Quantities of formoterol excreted in urine for male and female dogs that received the new formulation at the high doses were approximately 2 to 3 and 1.5 times quantities excreted by male and female dogs that received the old formulation, respectively.

In the initial IND submission dated April 27, 2000, the sponsor provided the study report of a 6-month inhalation toxicity study with magnesium stearate or magnesium stearate with lactose in Wistar rats. Deposited doses were estimated to be 0, 0.9, 20, 60, and 180 µg/kg/day. The study revealed no treatment-related abnormalities in the respiratory system. The 6-month NOAEL value for magnesium stearate in rats was 180 µg/kg/day with the inhalation route of exposure. In a letter from the Division dated August 17, 2000, the sponsor was asked to justify their selection of the rat as the most appropriate species for the 6-month inhalation toxicity study. Generally, species selection is based on short-term studies conducted in rodent and nonrodent species.

In Amendment #007 dated November 29, 2000 and Amendment #012 dated January 17, 2001, the sponsor provided summaries of 2- and 4-week inhalation toxicology studies with magnesium stearate in dogs.

In the 2-week repeat dose inhalation toxicity study, 1 dog/sex/group received magnesium stearate at doses of 0.038 and 3.35 mg/kg/day (There was no mention of a concurrent control group). Based upon a deposition factor of 0.17, deposited doses were estimated to be 0.007 and 0.6 mg/kg/day, respectively. Progressive reductions in food consumption and marked weight losses were observed for dogs at 0.6 mg/kg/day. Comparison of respiratory function parameters before and after dosing for dogs at 0.6 mg/kg/day found a small decrease of tidal volume with a concurrent increase in respiratory rate. Further, comparison of parameters for dogs at 0.6 mg/kg/day on treatment days 1 to 11, prior to dosing, with pretest data revealed a statistically significant reduction in tidal volume by day 11 with no change in respiratory rate. A similar change was observed for the male dog at 0.007 mg/kg/day. Eosinophilic intra-alveolar foreign bodies were evident in the lungs of both dogs at 0.6 mg/kg/day.

In the 4-week inhalation toxicity study, dogs were exposed to magnesium stearate aerosol concentrations of 0.017, 0.15, or 1.41 mg/L for 15, 30, or 60 min, respectively. Total doses for the low, mid, and high dose groups were estimated to be 0.09, 1.6, and 30.5 mg/kg/day, respectively. Based upon a deposition factor of 0.17, deposited doses are estimated to be 0.015, 0.27, and 5.2 mg/kg/day, respectively. A control group was exposed to chamber air for 60 min each day. The reversibility of any treatment-related effects, found during the treatment period, was assessed during a 4-week recovery period for air-control and high dose groups. The sponsor identified the high dose as the NOAEL.

There appear to be some inconsistencies between results of 2- and 4-week inhalation toxicity studies with dogs. With a deposited dose of 5.2 mg/kg/day in the 4-week study, there were no reported changes of lung function parameters or lung histopathology. In contrast, with a deposited dose of 0.6 mg/kg/day in the 2-week study, decreased tidal volume and eosinophilic intra-alveolar foreign bodies in the lungs were evident. The 2- and 4-week inhalation toxicity studies with dogs suggest that it was possible to administer higher doses of magnesium stearate to dogs as compared with rats, and to produce alterations of lung functional parameters and histology. Pulmonary effects were seen concomitantly with systemic effects of decreased food consumption and body weight. The sponsor should be requested to submit full reports of the 2- and 4-week inhalation toxicity studies with magnesium stearate in dogs.

**Safety evaluation:**

The sponsor conducted a 13-week bridging study with beagle dogs using the inhalation route to assess differences in the toxicity of a new formulation of formoterol with excipients, lactose and magnesium stearate, as compared to the older formulation of formoterol with lactose only. There were no differences in the toxicity profiles between the new and old formulations of formoterol. The deposited formoterol dose of 0.5 µg/kg/day for the new formulation could be considered the NOAEL given the sporadic nature of electrocardiographic changes and no histopathological findings at this dose. The dose of magnesium stearate at the NOAEL was 1 µg/kg/day.

In clinical use, the minimum (i.e., 1 puff) and maximum (i.e., 4 puffs) doses of formoterol are [redacted] and [redacted] µg/kg/day, respectively Minimum and maximum doses of magnesium stearate are [redacted] and [redacted] µg/kg/day, respectively. The NOAEL in the 13- b(4)

week bridging study with beagle dogs provides [redacted] and [redacted]fold margins of safety for minimum clinical daily doses of formoterol and magnesium stearate, respectively. Safety margins are less than 1 for maximum possible clinical daily doses of formoterol and magnesium stearate. However, control animals in the 13-week bridging study received a deposited dose of magnesium stearate at 9.7 µg/kg/day with no apparent adverse findings. b(4)

**Safety issues relevant to clinical use:** None.

**Other clinically relevant issues:** None.

**Conclusions:**

A 13-week bridging study with beagle dogs using the inhalation route found no differences in the toxicity profile of a new formulation of formoterol with excipients, lactose and magnesium stearate, as compared to the older formulation of formoterol with lactose only.

The sponsor should be requested to submit full reports of the 2- and 4-week inhalation toxicity studies with magnesium stearate in dogs.

**Communication review:**

Investigator's brochure/informed consent review: Not applicable.

**RECOMMENDATIONS:**

**Internal comments:** In the 2-week repeat dose inhalation toxicity study with magnesium stearate in dogs, decreased lung tidal volumes were evident with deposited doses of 0.007 and 0.6 mg/kg/day. Histopathological examination found eosinophilic intra-alveolar foreign bodies in the lungs at 0.6 mg/kg/day. These findings were not reproduced in a 4-week study. Nevertheless, dogs may be potentially more sensitive to any pulmonary toxicity induced by magnesium stearate as compared to rats.

**External recommendations (to sponsor):**

1. For the 13-week inhalation toxicity study in dogs (Reference Number 992022), the ratio of lactose to magnesium stearate was reported to be 200 to 1. It is not clear if this ratio was based on relative weights or some other parameter, because the reported doses of lactose + magnesium stearate and magnesium stearate are in an approximate 7.5 to 1 ratio rather than a 200 to 1 ratio. For Group 1 which received the placebo, doses of lactose + magnesium stearate and magnesium stearate were 427 and 57.158 µg/kg/day, respectively. The ratio of these doses is approximately 7.5 to 1 (the dose of 427 µg/kg/day includes both lactose and magnesium stearate).

a. Explain the discrepancy between the lactose to magnesium stearate ratio of 200 to 1 for the placebo formulation and the approximate ratio of 7.5 to 1 for administered doses.

b. Explain how the dose of 427 µg/kg/day for lactose + magnesium stearate administered to Group 1 was determined.

c. Clarify the basis for the ratio of 200 to 1 for lactose to magnesium stearate (e.g., weight).

2. For the 13-week inhalation toxicity study in dogs (Reference Number 992022) with regard to the new formulation (batch number 1V66501-9-0002), the ratio of magnesium stearate to foradil was reported to be 4.2 to 1. However, the ratio of the magnesium stearate dose to foradil dose for Groups 2, 3, and 4 was approximately 1.7 to 1. Explain the discrepancy between the magnesium stearate to foradil ratio of 4.2 to 1 for the drug batch and the ratio of 1.7 to 1 for administered doses.

3. Clarify the basis of the ratio of 1 to 828 to 4.2 for foradil to lactose to magnesium stearate (e.g., weight).

4. Submit full reports of the 2- and 4-week inhalation toxicity studies with magnesium stearate in dogs.

**Draft letter content for sponsor (if not same as above):**

**Future development or issues:** None.

**Reviewer signature:**

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

**Team leader signature** [concurrence/non-concurrence]:

Robin Huff, Ph.D. Date
Supervisory Pharmacologist, HFD-570

cc: list:
IND 60,254 Division File, HFD-570
JaniP, HFD-570
HuffR, HFD-570
RobisonT, HFD-570

**Studies reviewed within this submission:**

| Study | Report Number |
|---|---|
| 13-week bridging study in beagle dogs using the inhalation route to assess differences in the toxicity of a new formulation of formoterol as compared to an older formulation. | Sponsor Reference Number 992022 |
| Correspondence regarding 2- and 4-week inhalation toxicity studies in dogs. | |

**Studies not reviewed within this submission:** None.

**Introduction and drug history:**

The Foradil® Aerolizer (NDA 20-831) was recently approved. The new formulation in present IND differs from the formulation in NDA 20-831. The new formulation uses two excipients, lactose and magnesium stearate, while the old formulation used lactose only. Lactose is a well-known excipient for inhalation drug products and its safety has been established. Magnesium stearate has been used extensively as an excipient for oral drug products, but never as an excipient for inhalation drug products. Thus, inhalation use of magnesium stearate is a significant safety concern in the evaluation of the dry powder inhaler (DPI). This concern was conveyed to the sponsor in a pre-IND meeting held on June 30, 1999.

In the pre-IND meeting, the sponsor and the Division agreed to the following:

1. A 6-month inhalation toxicity to support the chronic inhalation use of magnesium stearate.
2. A 3-month bridging inhalation toxicity to compare the new formulation that contains excipients, lactose and magnesium stearate, with the old formulation that contains lactose only. This study should be completed prior to the start of phase 3 trials.
3. The above studies should be conducted in the most appropriate species and the sponsor will determine which species is most appropriate.

In the initial IND submission, the sponsor provided results of two inhalation toxicity studies in which rats were exposed to magnesium stearate for periods of 1 or 6 months. In the present IND submission, the sponsor has provided study results of a 3-month bridging inhalation toxicity study with dogs to compare the new and old formulations.

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TOXICOLOGY:

**Subchronic Toxicity**

**Dogs**

**Study title: 13-Week Inhalation Toxicity Study in Dogs.**

**Key study findings:**

•There were no differences in the toxicity profiles between the new formulation of formoterol with excipients, lactose and magnesium stearate, and the old formulation of formoterol with lactose only.

• The deposited formoterol dose of 0.5 µg/kg/day for the new formulation could be considered the NOAEL given the sporadic nature of electrocardiographic changes and no histopathological findings at this dose. The dose of magnesium stearate at the NOAEL was 1 µg/kg/day. Control animals in the 13-week bridging study received a deposited dose of magnesium stearate at 9.7 µg/kg/day with no apparent adverse findings.

•Electrocardiographic examinations found that heart rate was increased for male and female treatment groups receiving the new formulation (low, mid, and high doses) and old formulation. Decreased Q-T and P-Q intervals as well as increased P wave amplitudes were also observed and probably associated with increased heart rates. Incidences of altered T wave polarity were increased in a dose-related manner, and were particularly predominant for the new formulation at the high dose and the old formulation.

•There were no apparent treatment-related target organs of toxicity, although, papillary muscle fibrosis of the heart was observed for 1 male dog that received the new formulation at the mid dose.

**Study no:** Reference Number 992022
**Volume #, and page #:** Amendment #006
**Conducting laboratory and locatior**

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Novartis Pharma SA b(4)
Drug Metabolism and Pharmacokinetics
2-4 Rue Lionel Terry, BP 308
F-92506 Ruiel-Malmaison / Cedex

**Date of study initiation:** August 26, 1999 (Animals received)
**GLP compliance:** Yes
**QA report:** yes (X) no ( )
**Drug, lot #, radiolabel, and % purity:**
1. Placebo
Formoterol Fumarate DPI Placebo (Lactose / magnesium stearate [200:1]),
Batch number 1V66503-9-0002

2. New Formulation
Formoterol Fumarate 0.12% DPI (Foradil /lactose / magnesium stearate [1:828:4.2]) 0.12%)
Batch number 1V66501-9-0002 (Purity/Composition, 0.116% by HPLC)

3. Previous Formulation
Foradil /lactose [1:1000] 0.1%, (0.1% w/w Formoterol Fumarate blend in Lactose)
Batch numbers H9900001 (Purity/Composition, 101.3%) and X395 1199 (Purity/Composition, 101.7%)

It should be noted that the sponsor reported the drug purity differently for the new and previous formulations.

**Formulation/vehicle:** Formoterol was formulated in lactose/magnesium stearate (new formulation) or lactose (old formulation).

**Methods** (unique aspects): The sponsor conducted a 13-week bridging study with beagle dogs using the inhalation route to assess differences in the toxicity of a new formulation of formoterol with excipients, lactose and magnesium stearate, as compared to the older formulation of formoterol with lactose only.
**Dosing:**
*Species/strain:* Beagle dogs supplied by [redacted] b(4)
*#/sex/group or time point (main study):* 3 dogs/sex/group
*Satellite groups used for toxicokinetics or recovery:* None.
*Age:* Animals were 8.5 to 9.5 months old at the start of treatment.
*Weight:* The body weight range was 6.1 to 9.3 kg at the start of treatment.
*Doses in administered units:* The test and control articles were administered daily. Target aerosol concentrations (mg active compound/L air) were selected to achieve exposure durations of approximately 6 min (Group 2), 18 min (Group 3), and 60 min (Groups 4 and 5). Doses were increased gradually during the first week of treatment as described in the table below to achieve target doses. Treatment periods were 13 weeks and 4 days for male dogs and 13 weeks and 5 days for female dogs.

Groups/Formoterol Doses

| Group | Dose µg/kg/day | Test Article | Exposure time, min | Animal Numbers | |
|---|---|---|---|---|---|
| | | | | Male | Female |
| 1[b] | 0 | lactose / magnesium stearate | 60 | 1-3 | 16-18 |
| 2 | 3[a] | foradil / lactose / magnesium stearate | 6 | 4-6 | 19-21 |
| 3 | 10[a] | foradil / lactose / magnesium stearate | 18 | 7-9 | 22-24 |
| 4 | 30[a] | foradil / lactose / magnesium stearate | 60 | 10-12 | 25-27 |
| 5 | 30[a] | foradil / lactose | 60 | 13-15 | 28-30 |

a. In terms of active ingredient.
b. The controls were exposed to a 200:1 lactose / magnesium stearate blend using the same treatment duration and an aerosol concentration equivalent to the total (magnesium stearate + lactose) in Group 4.

$$\text{Estimated Inhaled Dose (µg/kg/day)} = \frac{\text{Concentration (µg/L)} \times \text{Minute Volume (L/min)} \times \text{Duration (min)}}{\text{Body weight (kg)}}$$

Target Doses were increased gradually during the first week of treatment as described in the table.

| Group | Days | Dose, µg/kg/day |
|---|---|---|
| Group 1 Control | Day 1 to Completion | 0 |
| Group 2 Low Dose of New Formulation | Day 1 to Completion | 3 |
| Group 3 Mid Dose of New Formulation | Days 1-2 | 3 |
| | Day 3 to Completion | 10 |
| Group 4 High Dose of New Formulation | Days 1-2 | 3 |
| | Days 3-4 | 10 |
| | Day 5 to Completion | 30 |
| Group 5 Old Formulation | Days 1-2 | 3 |
| | Days 3-4 | 10 |
| | Day 5 to Completion | 30 |

Estimated Achieved Dose Levels for Lactose / Magnesium Stearate in Group 1 and Formoterol in Groups 2 through 5.

| Group | Mean target dose[a], µg/kg/day | | Mean estimated dose, µg/kg/day | | Mean Percent, % | |
|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female |
| 1 | 427 | 427 | 458.7 | 435.14 | 107.3 | 102.4 |
| 2 | 3.0 | 3.0 | 3.4 | 3.3 | 113.6 | 110.9 |
| 3 | 10 | 10 | 11.2 | 10.1 | 111.9 | 100.8 |
| 4 | 30 | 30 | 32.5 | 34.5 | 108.3 | 115.0 |
| 5 | 30 | 30 | 30.1 | 28.5 | 100.3 | 95.0 |

Mean Estimated Magnesium Stearate Dose Levels

| Group | µg/kg/day | Aerosol Concentration µg Mg Stearate/L | Minute Volume L/min |
|---|---|---|---|
| 1 | 57.158[a] | 3.070 | 3.765 |
| 2 | 5.872 | 2.423 | 4.063 |
| 3 | 17.747 | 2.423 | 3.679 |
| 4 | 56.00 | 2.423 | 3.130 |
| 5 | - | - | - |

a. The ratio of lactose to magnesium stearate in the placebo formulation (batch number 1V66503-9-0002) was reported to be 200 to 1. For Group 1 which the received the placebo, doses of lactose + magnesium stearate and magnesium stearate were reported to be 427 and 57.158 µg/kg/day, respectively. The ratio of these doses is approximately 7.5 to 1 (it should be noted that the dose of 427 µg/kg/day includes both lactose and magnesium stearate). The sponsor should be asked to explain the discrepancy between the lactose to magnesium stearate ratio of 200 to 1 for the placebo formulation and the approximate ratio of 7.5 to 1 for doses.

Particle Size Distribution: Mean Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD).

| Group | Gravimetric | | Chemical | | Percentage of Particles < |
|---|---|---|---|---|---|
| | MMAD, µM | GSD | MMAD, µM | GSD | Gravimetric / Chemical |
| 1 | | | | | |
| 2, 3, and 4 | | | | | |
| 5 | | | | | |

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Deposited Doses for Lactose/Magnesium Stearate or Formoterol and Magnesium Stearate (for dogs, the estimated minute volume and body weight were 3.6 L/min and 10 kg, respectively).

| Group | Lactose/Mg Stearate or Formoterol | | Mg Stearate Dose Levels | |
|---|---|---|---|---|
| | Total Dose µg/kg/day | Deposited Dose[a] µg/kg/day | Total Dose µg/kg/day | Deposited Dose[a] µg/kg/day |
| 1 | 427 | 73 | 57.158 | 9.7 |
| 2[b] | 3.0 | 0.5 | 5.872 | 1 |
| 3[b] | 10 | 1.7 | 17.747 | 3 |
| 4[b] | 30 | 5 | 56.00 | 9.5 |
| 5 | 30 | 3.3 | - | |

a. For a —µm particle size (Groups 1, 2, 3, and 4), a deposition factor of 0.17 was used. For a —µm particle size (Group 5), a deposition factor of 0.11 was used.

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b. For the new formulation (batch number 1V66501-9-0002), the ratio of magnesium stearate to formoterol fumarate was reported to be 4.2 to 1. However, the ratio of the magnesium stearate dose to foradil dose for Groups 2, 3, and 4 was approximately 1.7 to 1. The sponsor should be asked to explain the discrepancy between the magnesium stearate to foradil ratio of 4.2 to 1 for the drug batch and the ratio of 1.7 to 1 for doses.

*Route, form, volume, and infusion rate:* Inhalation was by snout-only exposure. The sponsor reported that the snout-only design of the exposure system ensured a uniform distribution of the test article in the exposure chamber and provided a constant flow of

test article to each of four exposure ports. The flow of air at each exposure port was 10 L/min, which was reported to be sufficient to minimize re-breathing of the test atmosphere, as it was about twice the respiratory minute volume of a dog.

**Observations and times:**
*Clinical signs:* Dogs were monitored for mortality/moribundity twice per day. Animals were monitored during the exposure period and at least twice daily for clinical signs of toxicity.
*Body weights:* Body weights were measured weekly.
*Food consumption:* Food consumption was measured daily.
*Ophthalmoscopy:* Ophthalmic examinations were conducted at pretest and during weeks 4 and 13.
*EKG:* Electrocardiograms were recorded at pretest and during weeks 1, 4, and 13. During the treatment period, records were made prior to and 1 hr after dosing. Electrocardiograms were obtained using Einthoven (I, II, and III) and Goldberger (aVR, aVL, and aVF) leads. Heart rate, P wave duration and amplitude and P-Q, QRS, and Q-T intervals were measured using a representative section of the electrocardiogram from lead II.
*Hematology:* Blood for determination of hematology parameters was collected at pretest and in weeks 5 and 13.
*Clinical chemistry:* Blood for determination of clinical chemistry parameters was collected at pretest and in weeks 5 and 13.
*Urinalysis:* Urine for determination of urinalysis parameters was collected at pretest and in weeks 5 and 13.
*Gross pathology:* At the end of the treatment period, animals were sacrificed and submitted to necropsy examination.
*Organs weighed:* Absolute organ weights were obtained for the adrenal glands, brain (including brainstem), heart, kidneys, liver, lungs, pituitary gland, prostate gland, spleen, testes with epididymides, and thyroid gland with parathyroids.
*Histopathology:* Tissues and organs, listed in the histopathology inventory table, were fixed, processed, embedded, sectioned at a nominal thickness of 4 µm, stained with hematoxylin and eosin, and examined by light microscopy. One section of lungs was stained with Masson's trichrome stain. Bone marrow smears from the one sternum of each animal were collected for possible future examination.
*Toxicokinetics:* Blood for determination of plasma formoterol levels was collected from treatment groups on days 12 and 92 at 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hr after dosing. Blood was collected from control animals at 1 hr after dosing. Urine samples for measurement of formoterol levels were collected over a 24-hr period on days 8-9, 23-24, and 88-89 for male dogs and on days 13-14, 24-30, and 90-91 for female dogs. Following liquid-liquid extraction, formoterol levels in plasma and urine were quantified by HPLC/MS/MS using electrospray ionization as an interface.
*Other:* Respiratory function parameters (i.e., respiration rate, tidal volume, and minute volume) were measured at pretest and in weeks 1, 4, and 13. During the treatment period, records were made prior to test article administration. Data were used for estimation of target doses.

**Results:**

Results are discussed in terms of deposited dose. Deposited doses in terms of the active agent, foradil, were as follows: Control, 0 µg/kg/day; low dose of the new formulation, 0.5 µg/kg/day; mid dose of the new formulation, 1.7 µg/kg/day; high dose of the new formulation, 5 µg/kg/day, and dose of the old formulation, 3.3 µg/kg/day.

**Mortality:** None.

**Clinical signs:** General erythema (i.e., redness produced by congestion of capillaries) of general body surfaces and/or oral mucous membranes was observed in treatment groups. These observations occurred after the daily dosing period, while dogs were in their pens. Erythema may be attributed to $\beta_2$-receptor mediated peripheral vasodilation.

Males: For male dogs that received the new formulation at 0.5 µg/kg/day, general erythema of oral mucous membranes was observed during week 12 of treatment for 3 of 3 animals. For male dogs that received the new formulation at 1.7 µg/kg/day, general erythema of body surfaces was observed during weeks 1 and 2 for 2 of 3 animals and during week 12 for 1 of 3 animals. General erythema of oral mucous membranes was observed during week 1 for 2 of 3 animals, weeks 12 and 13 for 2 of 3 animals, and during week 14 for 1 of 3 animals. For male dogs that received the new formulation at 5 µg/kg/day, general erythema of body surfaces and oral mucous membranes was observed from weeks 1 to 14 for 3 of 3 animals. For male dogs that received the old formulation at 3.3 µg/kg/day, general erythema of body surfaces and oral mucous membranes was observed during weeks 1 to 5 for 3 of 3 animals, weeks 6 to 9 for 1 of 3 animals, week 10 for 2 of 3 animals, and weeks 11 to 14 for 2 of 3 animals.

Females: For female dogs that received the new formulation at 1.7 µg/kg/day, general erythema of body surfaces was observed during week 1 for 3 of 3 animals. General erythema of oral mucous membranes was observed during week 1 for 3 of 3 animals and during week 12 for 1 of 3 animals. For female dogs that received the new formulation at 5 µg/kg/day, general erythema of body surfaces and oral mucous membranes was observed from weeks 1 to 14 for 3 of 3 animals. For female dogs that received the old formulation at 3.3 µg/kg/day, general erythema of body surfaces was observed from weeks 1 to 2 for 3 of 3 animals, weeks 3 to 8 (minimal, sporadic) for 2 of 3 animals, and weeks 8 to 14 for 2 of 3 animals. General erythema of oral mucous membranes was observed from weeks 1 to 2 for 2 of 3 animals, weeks 3 to 8 (minimal, sporadic) for 2 of 3 animals, weeks 8 to 11 for 2 of 3 animals, and weeks 12 to 14 for 3 of 3 animals.

**Body weights:** There were no apparent changes in body weight gain during the treatment period. Body weights for male controls on days 1 and 96 were 8.4 and 8.6 kg, respectively, yielding a 2.4% increase of initial weights. Body weight was unchanged for male dogs that received the new formulation at 0.5 µg/kg/day. Body weights for male dogs that received the new formulation at 1.7 and 5 µg/kg/day were increased by 16.7 and 7.2% of initial weights. Body weights for male dogs that received the old formulation at 3.3 µg/kg/day were increased to 11.1% of initial weights. Body weights

for female controls on days 1 and 97 were 7.4 and 7.8 kg, respectively, yielding a 5.4% increase of initial weights. Body weights for female dogs that received the new formulation at 0.5, 1.7, and 5 µg/kg/day were increased to 5.6, 2.9, and 4.3% of initial weights, respectively. Body weights for female dogs that received the old formulation at 3.3 µg/kg/day were increased to 2.7% of initial weights.

**Food consumption:** Food consumption was transiently depressed during weeks 1/2 and 2/3 for male and female dogs that received that the new formulation at the high dose. The sponsor attributed this decreased food consumption, particularly in week 2, to exposure to 5 µg/kg/day following the dose escalation period. Food consumption during the treatment period was suppressed for female dogs that received the old formulation. For male dogs that received the new formulation at the high dose, food consumption during weeks 1/2 and 2/3 was decreased to 86.4 and 83.9% of control values (265 and 261 g/animal/day), respectively. For female dogs that received the new formulation at the high dose, food consumption during weeks 1/2 and 2/3 was decreased to 77.6 and 72.8% of control values (299 and 272 g/animal/day), respectively. Food consumption for female dogs that received the old formulation from weeks 1 to 14 was suppressed to 88.1% of the control (294 g/animal/day).

**Ophthalmoscopy:** Redness of the sclera was observed in treatment groups at weeks 4 and 13; however, incidences appeared to display little or no dose-response relationships. During week 4, redness of the sclera was observed with the new formulation at the low dose for 1 of 3 male dogs and 1 of 3 female dogs. During week 13, redness of sclera with the new formulation was observed as follows: low dose, 1 of 3 male dogs; mid dose, 2 of 3 female dogs; and high dose, 1 of 3 male dogs and 2 of 3 female dogs. During week 13, redness of the sclera with the old formulation was observed for 2 of 3 male dogs.

**Electrocardiography:** During weeks 1, 4, and 13, heart rate was increased for male and female treatment groups receiving the new formulation (low, mid, and high doses) and old formulation. Decreased Q-T and P-Q intervals as well as increased P wave amplitudes were also observed and probably associated with increased heart rates. The incidence of altered T wave polarity increased in a dose-related manner, and was particularly predominant for the new formulation at the high dose and the old formulation. For 1 female dog (#25) that received the new formulation at the high dose, second degree atrioventricular block was observed on days 5/6 at 1 hr after dosing. For 1 male dog (#14) that received the old formulation, a ventricular escape beat was observed on days 5/6 at 1 hr before dosing. For 1 female dog (#28) that received the old formulation, two consecutive ventricular premature complexes were observed on days 5/6 at 1 hr before dosing. Increased heart rate may be attributed to either stimulation of cardiac $\beta_1$- receptors or a compensatory response to $\beta_2$-receptor-mediated peripheral vasodilation.

ECG Parameters at Days 5/6 (Values in parentheses represent percent of before dosing value).

| Parameter | Sex | Before (B) or After (A) Dosing | Control | New Formulation | | | Old Formulation |
|---|---|---|---|---|---|---|---|
| | | | 0 µg/kg | 0.5 µg/kg | 1.7 µg/kg | 5 µg/kg | 3.3 µg/kg |
| Heart rate bpm | M | B | 93 | 83 | 80 | 83 | 97 |
| | | A | 90 | 123 (148%) | 147 (184%) | 233* (281%) | 237* (244%) |
| | F | B | 133 | 83* | 83* | 70* | 87* |
| | | A | 93 | 153* (184%) | 163* (196) | 160* (229%) | 183* (222%) |
| P amplitude mV | M | B | 0.27 | 0.18 | 0.17 | 0.15 | 0.22 |
| | | A | 0.23 | 0.23 | 0.22 | 0.27 (180%) | 0.33 (150%) |
| | F | B | 0.20 | 0.17 | 0.15 | 0.20 | 0.20 |
| | | A | 0.18 | 0.25 (147%) | 0.25 (167%) | 0.28 (140%) | 0.33 (165%) |
| P-Q Int. msec | M | B | 82 | 87 | 103 | 87 | 93 |
| | | A | 80 | 87 | 100 | 73 (84%) | 70 (75%) |
| | F | B | 78 | 93 | 83 | 90 | 93 |
| | | A | 80 | 90 | 77 | 87 | 80 (86%) |
| Q-T Interval msec | M | B | 190 | 207 | 213 | 210 | 193 |
| | | A | 200 | 197 | 193 | 157* (75%) | 157* (81%) |
| | F | B | 193 | 200 | 203 | 198 | 203 |
| | | A | 200 | 187 | 180* (89%) | 177* (89%) | 167* (82%) |

$p \leq 0.05$ (comparisons of control versus treatment and before and after dosing)

ECG Parameters at Week 4 (Values in parentheses represent percent of before dosing value).

| Parameter | Sex | Before (B) or After (A) Dosing | Control | New Formulation | | | Old Formulation |
|---|---|---|---|---|---|---|---|
| | | | 0 µg/kg | 0.5 µg/kg | 1.7 µg/kg | 5 µg/kg | 3.3 µg/kg |
| Heart rate bpm | M | B | 100 | 90 | 77 | 80 | 83 |
| | | A | 97 | 150 (167%) | 140 (182%) | 190* (238%) | 183* (221%) |
| | F | B | 100 | 97 | 97 | 83 | 93 |
| | | A | 90 | 120 (124%) | 153* (158%) | 153* (184%) | 197* (212%) |
| P amplitude mV | M | B | 0.23 | 0.17 | 0.15 | 0.17 | 0.25 |
| | | A | 0.22 | 0.28* (165%) | 0.20 | 0.22 | 0.38* (152%) |
| | F | B | 0.18 | 0.18 | 0.15 | 0.22 | 0.22 |
| | | A | 0.20 | 0.27 (150%) | 0.23 (153%) | 0.35 (159%) | 0.33 (150%) |
| P-Q Int. msec | M | B | 88 | 87 | 107* | 87 | 87 |
| | | A | 90 | 87 | 102 | 77 (89%) | 78 (90%) |
| | F | B | 80 | 103* | 87 | 92 | 98* |
| | | A | 83 | 92 (89%) | 77 (89%) | 85 (92%) | 73 (75%) |
| Q-T Interval msec | M | B | 198 | 203 | 205 | 203 | 187 |
| | | A | 195 | 185 (91%) | 180 (88%) | 167* (82%) | 167* (89%) |
| | F | B | 198 | 205 | 197 | 200 | 190 |
| | | A | 205 | 180 (88%) | 187 | 187 | 162* (85%) |

$p \leq 0.05$ (comparisons of control versus treatment and before and after dosing)

ECG Parameters at Week 13 (Values in parentheses represent percent of before dosing value).

| Parameter | Sex | Before (B) or After (A) Dosing | Control | New Formulation | | | Old Formulation |
|---|---|---|---|---|---|---|---|
| | | | 0 µg/kg | 0.5 µg/kg | 1.7 µg/kg | 5 µg/kg | 3.3 µg/kg |
| Heart rate bpm | M | B | 100 | 90 | 80 | 63 | 80 |
| | | A | 93 | 130 (144%) | 170* (212%) | 203* (322%) | 177* (221%) |
| | F | B | 100 | 90 | 133 | 77 | 83 |
| | | A | 107 | 123 (137%) | 157 (118%) | 123 (160%) | 120 (145%) |
| P amplitude mV | M | B | 0.25 | 0.22 | 0.18 | 0.13 | 0.22 |
| | | A | 0.23 | 0.25 | 0.27 (150%) | 0.25 (192%) | 0.38* (173%) |
| | F | B | 0.22 | 0.17 | 0.27 | 0.23 | 0.25 |
| | | A | 0.18 | 0.25 (147%) | 0.30 (111%) | 0.32 (139%) | 0.30 (120%) |
| P-Q Int. msec | M | B | 88 | 87 | 107* | 87 | 87 |
| | | A | 90 | 87 | 102 | 77 (88.5%) | 78 (89.7%) |
| | F | B | 80 | 103* | 87 | 92 | 98* |
| | | A | 83 | 92 | 77 | 85 | 73 |
| Q-T Interval msec | M | B | 187 | 193 | 200 | 213 | 200 |
| | | A | 193 | 180 (93%) | 177 (88.5%) | 167* (78%) | 167* (83.5%) |
| | F | B | 198 | 195 | 197 | 200 | 190 |
| | | A | 205 | 193 | 187 | 187 | 162* (85%) |

$p \leq 0.05$ (comparisons of control versus treatment and before and after dosing)

ECG Observations at Weeks 1, 4, and 13 (BD = Before Dosing and AD = After Dosing).

| Treatment Group | Animal # | Week | Observation |
|---|---|---|---|
| 0.5 µg/kg/day F+ MS + L | Male #6 | Wk1 AD, Wk 5 AD, and Wk 13 AD | Altered T wave polarity (negative compared with biphasic before dosing) |
| 1.7 µg/kg/day F + MS + L | Male #8 | Wk1 AD and Wk 13 AD | Altered T wave polarity (negative compared with biphasic before dosing) |
| | Male #9 | Wk 1 AD, Wk 4 AD, and Wk 13 AD | Minor ST depression (<0.2 mV) ST segment descending |
| | Female #24 | Wk 1 AD and Wk 4 AD | Altered T wave polarity (negative compared with biphasic or positive before dosing) |
| 5 µg/kg/day F + MS + L | Male #10 | Wk 1 AD and Wk 13 AD | Altered T wave polarity (negative compared with biphasic before dosing) |
| | Male #11 | Wk 1 AD, Wk 4 AD, and Wk 13 AD | Altered T wave polarity (negative compared with positive and/or biphasic before dosing) |
| | Male #12 | Wk 1 AD, Wk 4 AD, and Wk 13 AD | Altered T wave polarity (negative compared with positive and/or biphasic before dosing) |
| | Female #25 | Wk 1 AD | Second degree atrioventricular block, Altered T-wave polarity (negative compared with biphasic before dosing) |
| | Female #26 | Wk 1 AD, Wk 4 AD, and Wk 13 AD | Minor ST junction elevation (<0.2 mV) |
| | Female #27 | Wk 4 AD | Altered T wave polarity (positive compared with negative before dosing) |
| 3.3 µg/kg/day F + L | Male #14 | Wk 1 BD | Ventricular escape beat (1) |
| | | Wk 1 AD, Wk 13 AD | Altered T wave polarity (negative compared with biphasic before dosing) |

| | | | |
|---|---|---|---|
| | Female #28 | Wk 1 BD | Two consecutive ventricular premature complexes. |
| | | Wk 1 AD | Altered T wave polarity (negative compared with biphasic and positive before dosing). Minor depression of ST junction and ST segment (<0.2 mV) |
| | Female #29 | | Altered T wave polarity (negative compared with positive before dosing) |

F + MS + L = Formoterol + magnesium stearate + lactose
F + L = Formoterol + lactose

**Hematology:** The relationships of changes in hematology parameters to treatment were unclear, as changes were generally small and occurred principally in male treatment groups.

Week 5: Red blood cell counts for male dogs that received the new formulation at mid and high doses were decreased to 80.7 and 85.8% of the control (6.75 x $10^{12}$/L), respectively. Hemoglobin levels for male dogs that received the new formulation at mid and high doses and the new formulation were decreased to 83.6, 84.5, and 89.4% of the control (9.35 mmol/L), respectively. Hematocrit for male dogs that received the new formulation at mid and high doses and the new formulation were decreased to 83.7, 86, and 90.7% of the control (0.43), respectively. The mid reticulocyte fluorescence ratio for female dogs that received the old formulation was decreased to 38.7% of the control (16.8%).

Week 13: Red blood cell counts for male dogs that received the new formulation at low, mid, and high doses were decreased to 86, 84, and 84% of the control (7.27 x $10^{12}$/L), respectively. Hemoglobin levels for male dogs that received the new formulation at low, mid, and high doses and the old formulation were decreased to 87.3, 86.1, 80.5, and 88.1% of the control (10.05 mmol/L), respectively. Hematocrit for male dogs that received the new formulation at low, mid, and high doses and the old formulation were decreased to 87.2, 85.1, 80.9, and 89.4% of the control (0.47), respectively. Monocyte counts for male dogs that received the new formulation at the high dose and the old formulation were increased to 194.3 and 191.4% of the control (0.35 x 109/L), respectively. The mid reticulocyte fluorescence ratio for female dogs that received the old formulation was decreased to 39.4% of the control (18.0%).

**Clinical chemistry:** Potassium levels were increased at weeks 5 and 13 for male dogs that received the new formulation at low, mid, and high doses and the old formulation. Triglyceride levels were decreased at weeks 5 and 13 for male dogs that received the new formulation at mid and high doses and the old formulation.

Week 5: Potassium levels for male dogs that received the new formulation at low, mid, and high doses and the new formulation were increased to 110.5, 109.8, 109.1, and 130.7% of the control (4.30 mmol/L), respectively. Triglyceride levels for male dogs that received the new formulation at mid and high doses and the old formulation were decreased to 80, 58, and 86% of the control (0.50 mmol/L), respectively. Total lipids, cholesterol, and phospholipid levels for female dogs that

received the old formulation were increased to 116.3, 125.3, and 119.35% of control values (5.35 g/L, 3.76 mmol/L, and 4.29 mmol/L), respectively. Creatinine levels for female dogs that received the new formulation at the high dose and the old formulation were increased to 123.6 and 115.3% of the control (64.9 µmol/L), respectively. Relative γ-globulin levels for male dogs that received the new formulation at mid and high doses and the old formulation were increased to 112.7, 116.4, and 114.6% of the control (0.055), respectively. Absolute γ-globulin levels for male dogs that received the new formulation at the high dose and the old formulation were increased to 112.2 and 120.3% of the control (3.20 g/L), respectively. Alanine aminotransferase activities for female dogs that received the new and old formulations were increased to 120.8-141.7 and 162.5% of the control (0.48 µkat/L), respectively, although, no dose-response relationships were evident. Alkaline phosphatase activities for female dogs that received the new and old formulations were increased to 146.4-155.7 and 122% of the control (3.32 µkat/L), respectively, although, no dose-response relationships were evident.

Week 13: Potassium levels for male dogs that received the new formulation at low, mid, and high doses and the new formulation were increased to 112, 103.5, 107.8, and 114.1% of the control (4.33 mmol/L), respectively. Triglyceride levels for male dogs that received the new formulation at mid and high doses and the old formulation were decreased to 82.2, 66.7, and 77.8% of the control (0.50 mmol/L), respectively. Glucose levels for female dogs that received the new formulation at the high dose and the old formulation were decreased to 76.1 and 77.6% of the control (6.39 mmol/L), respectively. Creatinine levels for female dogs that received the new formulation at mid and high doses and the new formulation were increased to 148.4, 122.4, and 113.7% of the control (73.6 µmol/L), respectively. Alanine aminotransferase activities for female dogs that received the new and old formulations were increased to 118.2-145.5% and 150.9% of the control (0.55 µkat/L), respectively, although, no dose-response relationships were evident. Alkaline phosphatase activities for female dogs that received the new formulation were increased to 150.4-240.4% of the control (3.61 µkat/L), although, no dose-response relationships were evident.

**Urinalysis:** Urinary osmolality for female dogs that received the new formulation at the high dose or the old formulation were decreased to 82 and 72.8% of the control (925 mmol/kg), respectively.

**Organ weights:** Alterations in absolute and relative kidney and liver weights were observed for male dogs that received that old formulation. Changes in kidney weights may correspond to histopathological findings of interstitial nephritis.

Kidneys: Absolute left and right kidney weights for male dogs that received the old formulation were increased to 128.8 and 132.3% of control values (18.88 and 18.95 g), respectively. Relative left and right kidney weights for male dogs that received the old formulation were increased to 127 and 130.8% of control values (26.57 and 26.67% brain weight), respectively.

Liver: Absolute and relative liver weights for male dogs that received the old formulation were increased to 129.5 and 127.3% of control values (258.4 g and 363.5% brain weight), respectively.

**Gross pathology:** There were no treatment-related gross pathological findings.

**Histopathology:** There was no apparent treatment-related target organ of toxicity. Histopathological findings were observed in the heart and kidneys. Papillary muscle fibrosis was observed for 1 male dog that received the new formulation at 1.7 µg/kg/day, although, there was no dose-response relationship. Papillary muscle fibrosis has been reported in previous inhalation toxicity studies with dogs that received the $\beta_2$-adrenergic agent, formoterol, and appeared to be associated with increased heart rate, so this finding most likely has some relationship to treatment. Interstitial nephritis was observed for 1 male dog that received the old formulation at 3.3 µg/kg/day.

Histopathological findings for dogs that received formoterol in the new formulation at deposited doses of 0, 0.5, 1.7, and 5 µg/kg/day or in the old formulation at a deposited dose of 3.3 µg/kg/day.

| Organ/Tissue | Sex | Control | New Formulation | | | Old Formulation |
|---|---|---|---|---|---|---|
| | | | 0.5 µg/kg/day | 1.7 µg/kg/day | 5 µg/kg/day | 3.3 µg/kg/day |
| **Heart** | | | | | | |
| -papillary muscle fibrosis | M | 0 | 0 | 1 | 0 | 0 |
| | F | 0 | 0 | 0 | 0 | 0 |
| **Kidneys** | | | | | | |
| -interstitial nephritis | M | 0 | 0 | 0 | 0 | 1 |
| | F | 0 | 0 | 0 | 0 | 0 |

**Toxicokinetics:** Blood for measurement of plasma drug levels was collected on day 12 and during week 14. Urine for measurement of urinary drug excretion was collected on day 23 (males)/day 29 (females) and during week 13.

Plasma: For dogs that received the new formulation, plasma AUC values for formoterol generally increased with elevating dose, although, increases were less than proportional to dose. At week 14 for female dogs that received the new formulation at doses of 0.5 and 1.7 µg/kg/day, there were no differences in plasma AUC values for formoterol. Plasma AUC values for formoterol in male and female dogs that received the new formulation at the high dose were, in general, approximately 1.5 times the values observed in male and female dogs that received the old formulation. However, for female dogs at week 14, plasma AUC values obtained with the old formulation were approximately 2 times those obtained with the new formulation at the high dose.

Urine: For female dogs at day 29 and male dogs at week 13 that received the new formulation, quantities of formoterol excreted in the urine at the mid and high doses were approximately proportional to the 3-fold change in dose. However, quantities excreted at the low dose were smaller than expected based upon mid and high doses. For male dogs at day 23 and female dogs at week 13 that received the new formulation, quantities of formoterol excreted in the urine at low and mid doses were

approximately proportional to the 3-fold change in dose. However, quantities excreted at the high dose were greater than expected based upon low and mid doses. Quantities of formoterol excreted in urine for male and female dogs that received the new formulation at the high doses were approximately 2 to 3 and 1.5 times quantities excreted by male and female dogs that received the old formulation, respectively.

Exposure of the Control Group: There was evidence that the control group received slight exposure to the test article based upon plasma samples obtained on day 12 and during week 14 as well as urine samples obtained on day 23/29 and during week 13. Plasma drug levels were detected for one male control on day 12 and two male controls during week 14. The plasma drug level in one control male on day 12 at 1 hr after dosing was 6.8% of the $C_{max}$ for the low dose group. Plasma drug levels in two control males during week 14 at 1 hr after dosing were 15.3% of the $C_{max}$ for the low dose group. Urinary excretion of drug was detected for all male and female controls. Urinary quantities of drug excreted for male controls on day 23 and female controls on day 29 and during week 13 were 4.1 to 4.75% of quantities excreted by corresponding low dose groups. Urinary quantities of drug excreted for male controls during week 13 were 38.4% of quantities excreted by the low dose male group. However, it should be noted that the quantities of drug excreted by the low dose male group during week 13 were unusually low. Slight exposure of the control group to the test article appeared to have no significant effects on the results of the study.

**Table 2-1.: Mean toxicokinetic parameters of formoterol in plasma and urine**

Mean (n=3) of AUC, $C_{max}$ and Ae, range of $t_{max}$

| | Day 12, 23 or 29 [a] | | | | Week 13 or 14 [b] | | | |
|---|---|---|---|---|---|---|---|---|
| | Novel formulation | | | Previous formul. | Novel formulation | | | Previous formul. |
| Dose [c] | 3 | 10 | 30 | 30 | 3 | 10 | 30 | 30 |
| **Male dogs** | | | | | | | | |
| AUC [d] | 2.86 | 15.2 | 65.2 | 43.4 | 1.49 | 5.45 | 77.4 | 48.1 |
| $C_{max}$ [nmol/L] | 0.601 | 1.82 | 12.3 | 7.59 | 0.338 | 0.666 | 12.3 | 8.84 |
| $t_{max}$ [h] | 0.25–2 | 1–2 | 0.25–4 | 0.25-1 | 0.25–0.25 | 0.5-2 | 0.25-2 | 0.25-0.25 |
| $A_e$ [nmol] [e] | 3.30 | 8.42 | 42.1 | 22.7 | 0.384 | 11.3 | 33.4 | 11.2 |
| **Female dogs** | | | | | | | | |
| AUC [d] | 3.12 | 11.7 | 52.5 | 34.3 | 6.94 | 6.13 | 39.5 | 73.1 |
| $C_{max}$ [nmol/L] | 0.673 | 2.46 | 9.28 | 6.10 | 1.43 | 0.822 | 5.76 | 15.3 |
| $t_{max}$ [h] | 0.25-0.5 | 0.25-0.25 | 0.25-0.5 | 0.5-1 | 0.25-0.25 | 0.25-0.25 | 0.25-0.25 | 0.25-0.25 |
| $A_e$ [nmol] [e] | 1.94 | 9.06 | 22.5 | 16.7 | 2.27 | 5.43 | 26.8 | 14.7 |

a) Day 12 for AUC, $C_{max}$ and $t_{max}$,Day 23 for $A_e$ of male dogs, Day 29 for $A_e$ of female dogs

b) Week 14 for AUC, $C_{max}$ and $t_{max}$, Week 13 for Ae

c) Target dose level of Foradil (formoterol fumarate) in µg/kg/day

d) AUC(0-24h) in (nmol/L)h

e) Amount excreted in urine over 24 h

## 5.1. Group control

**Table 5.1-1.: Concentration of formoterol in dog plasma and excreted amounts in dog urine (Group control)**

| Sex | Dog Nbr | Plasma concentrations of Formoterol (nmol/L) | | Amounts of Formoterol (nmol) in urine | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Day12/1h | Week14/1h | D23/24h | | | Week 13/24h | | |
| | | | | Conc (nmol/L) | Volume (L) | Amount excreted (nmol) | Conc (nmol/L) | Volume (L) | Amount excreted (nmol) |
| M | 1 | 0.0407 | 0.0426 | 1.95 | 0.098 | 0.191 | 1.19 | 0.175 | 0.208 |
| M | 2 | 0.000 | 0.0605 | 1.69 | 0.080 | 0.135 | 1.17 | 0.146 | 0.1708 |
| M | 3 | 0.000 | 0.000 | 0.925 | 0.087 | 0.0805 | 1.16 | 0.055 | 0.0638 |
| | | D12/1h | Week14/1h | D29/24h | | | Week 13/24h | | |
| F | 16 | 0.000 | 0.000 | 0.950 | 0.095 | 0.0903 | 0.889 | 0.114 | 0.101 |
| F | 17 | 0.000 | 0.000 | 0.888 | 0.071 | 0.0630 | 0.977 | 0.094 | 0.0918 |
| F | 18 | 0.000 | 0.000 | 1.47 | 0.066 | 0.0970 | 1.15 | 0.114 | 0.131 |

LOQ = 0.0298 nmol/L (plasma) and 0.350 nmol/L (urine)

**Summary of individual study findings:**

The sponsor conducted a 13-week bridging study with beagle dogs using the inhalation route to assess differences in the toxicity of a new formulation of formoterol in combination with excipients, lactose and magnesium stearate, as compared to the older formulation of formoterol in combination with lactose only. Total doses of the new formulation for low, mid, and high dose groups were 3, 10, and 30 µg/kg/day, respectively. Deposited formoterol doses of the new formulation for the low, mid, and high dose groups were 0.5, 1.7, and 5 µg/kg/day, respectively. The total and deposited doses for the old formulation were 30 and 3.3 µg/kg/day, respectively. The control group was exposed to a combination of lactose and magnesium stearate at an aerosol concentration that was equivalent to the group that received the new formulation at the high dose.

The deposited formoterol dose of 0.5 µg/kg/day could be considered the NOAEL given the sporadic nature of electrocardiographic changes and no histopathological findings at this dose. The dose of magnesium stearate at the NOAEL was 1 µg/kg/day. Control animals received a deposited dose of magnesium stearate at 9.7 µg/kg/day with no apparent adverse findings.

Electrocardiographic examinations during weeks 1, 4, and 13 found that heart rate was increased for male and female treatment groups receiving the new formulation (low, mid, and high doses) and old formulation. Decreased Q-T and P-Q intervals as well as increased P wave amplitudes were also observed and probably associated with increased heart rates. Incidences of altered T wave polarity were increased in a dose-related manner, and were particularly predominant for the new formulation at the high dose and the old formulation. Increased heart rate may be attributed to either

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stimulation of cardiac $\beta_1$-receptors or a compensatory response to $\beta_2$-receptor-mediated peripheral vasodilation.

There were no apparent treatment-related target organs of toxicity, although, papillary muscle fibrosis of the heart was observed for 1 male dog that received the new formulation at the mid dose. Papillary muscle fibrosis has been reported in previous inhalation toxicity studies with dogs that received the $\beta_2$-adrenergic agent, formoterol, and appeared to be associated with increased heart rate, so this finding most likely has some relationship to treatment.

Blood for measurement of plasma drug levels was collected on day 12 and during week 14. Urine for measurement of urinary drug excretion was collected on day 23 (males)/day 29 (females) and during week 13. Plasma AUC values for formoterol in male and female dogs that received the new formulation at the high dose were, in general, approximately 1.5 times the values observed in male and female dogs that received the old formulation, possibly reflecting the same proportional difference in deposited dose. Quantities of formoterol excreted in urine for male and female dogs that received the new formulation at the high doses were approximately 2 to 3 and 1.5 times quantities excreted by male and female dogs that received the old formulation, respectively.

**Chronic Toxicity**

**Rats**

**Correspondence with Sponsor regarding the 6-Month Inhalation Toxicity Study with Magnesium Stearate and Lactose in Rats (Study # [redacted] 724353):** In the initial IND submission dated April 27, 2000, the sponsor provided study reports of a 1-month inhalation toxicity study with magnesium stearate in Wistar rats, and a 6-month inhalation toxicity study with magnesium stearate or magnesium stearate with lactose in Wistar rats. For the 6-month inhalation toxicity study, total doses of magnesium stearate were 0, 9.3, 200, 600, and 1800 µg/kg/day. Using a deposition factor of 0.10, deposited doses were 0, 0.9, 20, 60, and 180 µg/kg/day, respectively. The 0.9 µg/kg/day group was also exposed to 90 µg/kg/day of lactose monohydrate. The study revealed no treatment-related abnormalities in the respiratory system. The 6-month NOAEL value for magnesium stearate in rats was 180 µg/kg/day with the inhalation route of exposure. In a letter from the Division dated August 17, 2000, the sponsor was asked to justify their selection of the rat as the most appropriate species for the 6-month inhalation toxicity study. Generally, species selection is based on short-term studies conducted in rodent and nonrodent species. b(4)

**Sponsor's Response:**

In Amendment #007 dated November 29, 2000, the sponsor reported that two short-term inhalation toxicity studies with magnesium stearate had been conducted in dogs by [redacted]. The first study with magnesium stearate was composed of a dose escalation study followed by a subsequent 2-week repeat dose toxicity study. The maximum dose achieved in the dose escalation phase was 10 mg/kg/day. The second study with magnesium stearate was a 4-week repeat dose b(4)

inhalation toxicity study in which maximum dose levels of 37 mg/kg/day were achieved. The sponsor reported that administration of magnesium stearate produced no pathological evidence of toxicity in either study. The Division subsequently requested that the sponsor provide full reports for these two studies.

In Amendment #012 dated January 17, 2001, the sponsor provided summaries of these two studies.

The first study was composed of a dose escalation study followed by a 2-week repeat dose toxicity study. Magnesium stearate was administered by inhalation to beagle dogs using an oropharyngeal tube. In the dose escalation phase, two beagle dogs (1 male and 1 female) were treated with magnesium stearate by inhalation administration at doses of 0.168 mg/kg/day on day 1, 1.648 mg/kg/day on days 2 to 4, 3.29 mg/kg/day on day 5, and 10.01 mg/kg/day on days 6 to 9. In a 2-week repeat dose inhalation toxicity study, 1 dog/sex/group received magnesium stearate at doses of 0.038 and 3.35 mg/kg/day (There was no mention of a concurrent control group).

For the dose escalation study, there were treatment-related clinical signs or effects on body weight gain and food consumption. Eosinophilic intra-alveolar foreign bodies were evident in the lungs of the female dog.

For the 2-week inhalation toxicity study, there were no treatment-related clinical signs of toxicity. Progressive reductions in food consumption and marked weight losses were observed for dogs at 3.35 mg/kg/day. No electrocardiographic changes were evident for dogs at 0.038 or 3.35 mg/kg/day. Comparison of respiratory function parameters before and after dosing for dogs at 3.35 mg/kg/day found a small decrease of tidal volume with a concurrent increase in respiratory rate. Further, comparison of parameters for dogs at 3.35 mg/kg/day on treatment days 1 to 11, prior to dosing, with pretest data revealed a statistically significant reduction in tidal volume by day 11 with no change in respiratory rate. A similar change was observed for the male dog at 0.038 mg/kg/day. There were no apparent changes in hematology, clinical biochemistry, or urinalysis parameters. Eosinophilic intra-alveolar foreign bodies were evident in the lungs of both dogs at 3.35 mg/kg/day. Acute hepatitis (Hepatitis purulenta), purulent practitis, and acute lymphadenitis of the mesenteric, retropharyngeal, iliac, and pancreatic lymph nodes were evident in the female dog at 3.35 mg/kg/day.

In the 4-week inhalation toxicity study, dogs were exposed to magnesium stearate aerosol concentrations of 0.017, 0.15, or 1.41 mg/L for 15, 30, or 60 min, respectively. A control group was exposed to chamber air for 60 min each day. A total of 32 dogs were used in the study. The reversibility of any treatment-related effects, found during the treatment period, was assessed during a 4-week recovery period for air-control and high dose groups. The sponsor reported that there were no treatment-related changes evident with clinical signs, body weight, food consumption, ophthalmic examination, electrocardiographic examination, respiratory parameters, or laboratory investigations. Following the 4-week treatment period, increased thyroid and ovary weights were observed for female dogs of the high dose group; however, there were no corresponding histopathological findings in these tissues. There was no evidence of

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respiratory tract lesions. Following the 4-week recovery period, increased organ weights were no longer evident. The sponsor identified the high dose as the NOAEL.

**Evaluation:**

For the dose escalation study, based upon a deposition factor of 0.17, deposited doses for dogs were estimated to be 0.03, 0.3, 0.6, and 1.7 mg/kg/day, respectively. For the 2-week inhalation toxicity study, based upon a deposition factor of 0.17, deposited doses were estimated to be 0.007 and 0.6 mg/kg/day, respectively.

For the 4-week inhalation toxicity study in dogs, total doses for the low, mid, and high dose groups are estimated to be 0.09, 1.6, and 30.5 mg/kg/day, respectively. Based upon a deposition factor of 0.17, deposited doses are estimated to be 0.015, 0.27, and 5.2 mg/kg/day, respectively. The sponsor identified the NOAEL as the deposited dose of 5.2 mg/kg/day.

There appear to be some inconsistencies between results of 2- and 4-week inhalation toxicity studies. With a deposited dose of 5.2 mg/kg/day in the 4-week study, there were no reported changes of lung function parameters or lung histopathology. In contrast, with a deposited dose of 0.6 mg/kg/day in the 2-week study, decreased tidal volume and eosinophilic intra-alveolar foreign bodies in the lungs were evident. The sponsor should be requested to submit full reports of the 2- and 4-week inhalation toxicity studies with magnesium stearate in dogs.

The 2- and 4-week inhalation toxicity studies with dogs suggest that it was possible administer higher doses of magnesium stearate to dogs as compared with rats, and to produce alterations of lung functional parameters and histology. Pulmonary effects were seen concomitantly with systemic effects of decreased food consumption and body weight.

**Toxicology summary:**

The sponsor conducted a 13-week bridging study with beagle dogs using the inhalation route to assess differences in the toxicity of a new formulation of formoterol in combination with excipients, lactose and magnesium stearate, as compared to the older formulation of formoterol in combination with lactose only. Total doses of the new formulation for low, mid, and high dose groups were 3, 10, and 30 µg/kg/day, respectively. Deposited doses of the new formulation for the low, mid, and high dose groups were 0.5, 1.7, and 5 µg/kg/day, respectively. The total and deposited doses for the old formulation were 30 and 3.3 µg/kg/day, respectively. The control group was exposed to a combination of lactose and magnesium stearate at an aerosol concentration that was equivalent to the group that received the new formulation at the high dose.

The deposited formoterol dose of 0.5 µg/kg/day could be considered the NOAEL given the sporadic nature of electrocardiographic changes and no histopathological findings at this dose. The dose of magnesium stearate at the NOAEL was 1 µg/kg/day. Control animals received a deposited dose of magnesium stearate at 9.7 µg/kg/day with no apparent adverse findings.

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Electrocardiographic examinations during weeks 1, 4, and 13 found that heart rate was increased for male and female treatment groups receiving the new formulation (low, mid, and high doses) and old formulation. Decreased Q-T and P-Q intervals as well as increased P wave amplitudes were also observed and probably associated with increased heart rates. Incidences of altered T wave polarity were increased in a dose-related manner, and were particularly predominant for the new formulation at the high dose and the old formulation. Increased heart rate may be attributed to either stimulation of cardiac $\beta_1$-receptors or a compensatory response to $\beta_2$-receptor-mediated peripheral vasodilation.

There were no apparent treatment-related target organs of toxicity, although, papillary muscle fibrosis of the heart was observed for 1 male dog that received the new formulation at the mid dose. Papillary muscle fibrosis has been reported in previous inhalation toxicity studies with dogs that received the $\beta_2$-adrenergic agent, formoterol, and appeared to be associated with increased heart rate, so this finding most likely has some relationship to treatment.

Blood for measurement of plasma drug levels was collected on day 12 and during week 14. Urine for measurement of urinary drug excretion was collected on day 23 (males)/day 29 (females) and during week 13. Plasma AUC values for formoterol in male and female dogs that received the new formulation at the high dose were, in general, approximately 1.5 times the values observed in male and female dogs that received the old formulation, possibly reflecting the same proportional difference in deposited dose. Quantities of formoterol excreted in urine for male and female dogs that received the new formulation at the high doses were approximately 2 to 3 and 1.5 times quantities excreted by male and female dogs that received the old formulation, respectively.

In the initial IND submission dated April 27, 2000, the sponsor provided the study report of a 6-month inhalation toxicity study with magnesium stearate or magnesium stearate with lactose in Wistar rats. Deposited doses were estimated to be 0, 0.9, 20, 60, and 180 µg/kg/day. The study revealed no treatment-related abnormalities in the respiratory system. The 6-month NOAEL value for magnesium stearate in rats was 180 µg/kg/day with the inhalation route of exposure. The NOAEL was determined to be — fold greater than the expected exposure in humans (projected exposure was — µg/kg/day based upon —% magnesium stearate and 8 actuations per day; the current formulation is only —% magnesium stearate and may be used for only 4 actuations/day, resulting in a quadrupling of the safety margin). In a letter from the Division dated August 17, 2000, the sponsor was asked to justify their selection of the rat as the most appropriate species for the 6-month inhalation toxicity study. Generally, species selection is based on short-term studies conducted in rodent and nonrodent species. b(4)

In Amendment #007 dated November 29, 2000 and Amendment #012 dated January 17, 2001, the sponsor provided summaries of 2- and 4-week inhalation toxicology studies with magnesium stearate in dogs.

In the 2-week repeat dose inhalation toxicity study, 1 dog/sex/group received magnesium stearate at doses of 0.038 and 3.35 mg/kg/day (There was no mention of a concurrent control group). Based upon a deposition factor of 0.17, deposited doses were estimated to be 0.007 and 0.6 mg/kg/day, respectively. Progressive reductions in food consumption and marked weight losses were observed for dogs at 0.6 mg/kg/day. Comparison of respiratory function parameters before and after dosing for dogs at 0.6 mg/kg/day found a small decrease of tidal volume with a concurrent increase in respiratory rate. Further, comparison of parameters for dogs at 0.6 mg/kg/day on treatment days 1 to 11, prior to dosing, with pretest data revealed a statistically significant reduction in tidal volume by day 11 with no change in respiratory rate. A similar change was observed for the male dog at 0.007 mg/kg/day. Eosinophilic intra-alveolar foreign bodies were evident in the lungs of both dogs at 0.6 mg/kg/day.

In the 4-week inhalation toxicity study, dogs were exposed to magnesium stearate aerosol concentrations of 0.017, 0.15, or 1.41 mg/L for 15, 30, or 60 min, respectively. Total doses for the low, mid, and high dose groups are estimated to be 0.09, 1.6, and 30.5 mg/kg/day, respectively. Based upon a deposition factor of 0.17, deposited doses are estimated to be 0.015, 0.27, and 5.2 mg/kg/day, respectively. A control group was exposed to chamber air for 60 min each day. The reversibility of any treatment-related effects, found during the treatment period, was assessed during a 4-week recovery period for air-control and high dose groups. The sponsor identified the high dose as the NOAEL.

There appear to be some inconsistencies between results of 2- and 4-week inhalation toxicity studies. With a deposited dose of 5.2 mg/kg/day in the 4-week study, there were no reported changes of lung function parameters or lung histopathology. In contrast, with a deposited dose of 0.6 mg/kg/day in the 2-week study, decreased tidal volume and eosinophilic intra-alveolar foreign bodies in the lungs were evident. The 2- and 4-week inhalation toxicity studies with dogs suggest that it was possible administer higher doses of magnesium stearate to dogs as compared with rats, and to produce alterations of lung functional parameters and histology. Pulmonary effects were seen concomitantly with systemic effects of decreased food consumption and body weight. The sponsor should be requested to submit full reports of the 2- and 4-week inhalation toxicity studies with magnesium stearate in dogs.

**Toxicology conclusions:**

The sponsor conducted a 13-week bridging study with beagle dogs using the inhalation route to assess differences in the toxicity of a new formulation of formoterol in combination with excipients, lactose and magnesium stearate, as compared to the older formulation of formoterol in combination with lactose only. There were no differences in the toxicity profiles between the new and old formulations of formoterol.

The sponsor should be requested to submit full reports of the 2- and 4-week inhalation toxicity studies with magnesium stearate in dogs.

**Histopathology Inventory for IND # 60,254**

| Study | Sponsor Reference No. 992022 |
|---|---|
| Species | 13-Week Oral Toxicology Study in Dogs |
| Adrenals | X* |
| Aorta | X |
| Bone Marrow smear | Collected from sternum, not analyzed |
| Bone (femur) | X |
| Bronchi | X |
| Brain | X* |
| Cecum | X |
| Cervix | X |
| Colon | X |
| Duodenum | X |
| Epididymis | X* |
| Esophagus | X |
| Eye | X |
| Fallopian tube | |
| Gall bladder | X |
| Gross lesions | X |
| Harderian gland | |
| Heart | X* |
| Ileum | X |
| Injection site | |
| Jejunum | X |
| Kidneys | X* |
| Lachrymal gland | |
| Larynx | X |
| Liver | X* |
| Lungs | X* |
| Lymph nodes, cervical | |
| Lymph nodes mandibular | |
| Lymph nodes, mesenteric | X |
| Lymph nodes, retropharyngeal | X |
| Lymph nodes, medial tracheobronchial | X |
| Mammary Gland | X |
| Nasal cavity (4 levels) | X |
| Optic nerves | X |
| Ovaries | X |
| Pancreas | X |

| | |
|---|---|
| Parathyroid | X* |
| Peripheral nerve | |
| Pharynx | X |
| Pituitary | X* |
| Prostate | X* |
| Rectum | X |
| Salivary gland | X |
| Sciatic nerve | X |
| Seminal vesicles | |
| Skeletal muscle | X |
| Skin | X |
| Spinal cord | X |
| Spleen | X* |
| Sternum | |
| Stomach | X |
| Testes | X* |
| Thymus | X* |
| Thyroid | X |
| Tongue | X |
| Trachea | X |
| Urinary bladder | X |
| Uterus | X |
| Vagina | X |
| Zymbal gland | |
| Standard List | |
| | |

X, histopathology performed
*, organ weight obtained

APPEARS THIS WAY
ON ORIGINAL

/s/
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Timothy Robison
4/2/01 09:11:49 AM
PHARMACOLOGIST

Robin Huff
4/2/01 10:26:15 AM
PHARMACOLOGIST
Comments 1 - 3 already conveyed by facsimile. Comment 4 still needs t
o be conveyed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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Timothy Robison
9/29/03 02:51:34 PM
PHARMACOLOGIST

Joseph Sun
9/29/03 06:19:56 PM
PHARMACOLOGIST
I concur.