

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-949

PHARMACOLOGY REVIEW

INTEROFFICE MEMO

TO: NDA 21949
FROM: C. Joseph Sun, Ph. D., Supervisory Pharmacologist
Division of Pulmonary and Allergy Products
DATE: May 22, 2006

I concur with pharmacologist's recommendation that pharmacology and toxicology of budesonide have been adequately studied and the drug is approvable from a preclinical standpoint.

Pharmacology: The anti-inflammatory actions of budesonide are typical for its class and did not distinguish it from other glucocorticoids. Its anti-inflammatory activity in rat ear edema assay was demonstrated. It also inhibited airway inflammation mediated by antigen challenge or other mediators in several animal models.

General toxicity: Chronic inhalation toxicity studies (up to 12 months) in rats and dogs, subcutaneous toxicity study (6 months) in rats and oral toxicity study (6 months) in monkeys were conducted. Typical systemic glucocorticoid effects were observed. Some effects in the respiratory tree (accumulation of alveolar macrophages, pulmonary perivascular lymphocyte infiltration and increased mucus production) following inhalation administration were reported in rats whereas no local respiratory tract effects were observed in dogs.

Reproductive toxicity: Budesonide was teratogenic and embryocidal in rabbits and rats by subcutaneous administration. However, it was not teratogenic or embryocidal in rats by inhalation administration. Furthermore, epidemiological data indicated no risk to human during pregnancy. Thus, pregnancy category B is appropriate for the product.

Genotoxicity: It was not mutagenic nor clastogenic in Ames test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, recessive lethal test in *Drosophila melanogaster* and DNA repair analysis in rat hepatocyte.

Carcinogenicity: Three 2-year oral carcinogenicity studies were conducted in rats. Budesonide caused increases in the incidence of glioma in one study which was not confirmed in two subsequent studies. It produced hepatocellular tumors, typical of other glucocorticoids. No effects were reported in a 91-week oral carcinogenicity study in mice.

Labeling: Carcinogenesis, mutagenesis and impairment of fertility and pregnancy category B sections have been revised to incorporate the above-mentioned preclinical findings.

There are no outstanding preclinical issues.

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/s/

Joseph Sun
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PHARMACOLOGIST

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-949
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	9/12/05
PRODUCT:	Pulmicort Turbuhaler
INTENDED CLINICAL POPULATION:	Asthmatics
SPONSOR:	AstraZeneca
DOCUMENTS REVIEWED:	Vol. NA.
REVIEW DIVISION:	Division of Pulmonary and Allergy Products
PHARM/TOX REVIEWER:	Lawrence F. Sancilio, Ph.D.
PHARM/TOX SUPERVISOR:	Chng-long J. Sun, Ph.D.
DIVISION DIRECTOR:	Badrul Chowdhury, M.D., Ph.D.
PROJECT MANAGER:	Colette Jackson

Date of review submission to Division File System (DFS): 5/19/06

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EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability
Recommend approval.
- B. Recommendation for nonclinical studies
None.
- C. Recommendations on labeling
Modify the preclinical section to conform to the current labeling format.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The toxicity profile in rats, dogs and monkeys was characteristic of glucocorticoids. There was decreased organ weight or atrophy of the adrenal glands, thymus and other lymphoid organs. Rats and monkeys showed a decrease in body weight gained in contrast to an increase in body weight gain for dogs. Further manifestation of adrenal suppression occurred in monkeys where there were decreased urinary cortisol levels and decreased plasma cortisol levels in dogs. Typical glucocorticoid effects were observed following administration by the inhaled route. No histopathology was observed in the respiratory tract of dogs following administration by the inhaled route. However, in the one year inhalation study in rats, there was evidence of local effects (accumulation of alveolar macrophages, pulmonary perivascular lymphocyte infiltration and increased mucus production in the trachea).

In reproductive studies in rats by the subcutaneous route, there were decreased prenatal viability and viability of the young, at birth and during lactation. Subcutaneous administration to rats during gestation resulted in an increase in fetal loss and fetal abnormalities. This was not seen in rats when administered by the inhaled route. In rabbits, budesonide by the subcutaneous route produced fetotoxicity and teratogenicity.

The human epidemiology data with inhaled budesonide submitted by the sponsor indicate no risk for using the inhaled budesonide during early pregnancy. Consequently, category B in the Pregnancy subsection of the Precautions sections as indicated in NDA 20-441 is appropriate for this product.

Budesonide was not genotoxic in the following assays: Ames, Mouse Lymphoma, Human Lymphocyte Chromosomal Aberration, DNA- Repair Rat Hepatocyte, Mouse Micronucleus and the Sex-Linked Recessive Lethality Test in *Drosophila Melanogaster*.

Four carcinogenicity studies were conducted in mice and rats whereby the budesonide was administered in the drinking water. No carcinogenicity was observed in mice. In the first study, an increased incidence of gliomas was observed in male rats. However, this was not confirmed in two subsequent rat carcinogenicity studies. Like other glucocorticoids budesonide produced an increased incidence of hepatocellular tumors in rats.

B. Pharmacologic activity

Budesonide is a potent glucocorticoid based on its binding affinity capacity to the glucocorticoid receptor. Budesonide in in vitro studies inhibited LPS-induced TNF- α release from rat alveolar macrophages, mutagen-induced proliferation of lymphocytes from asthmatics, cytokine secretion from activated human alveolar macrophages and human epithelial and endothelial cells. In activated mononuclear cells from atopic patients, budesonide inhibited activation of T-cells, the release of chemotactic factors for eosinophils, the release of IL-3 and IL-5 and the chemotactic response of eosinophils to human IL-3 and IL-5. In challenged sensitized animals, budesonide instilled in the trachea suppressed the late phase exudative response in guinea pigs, and in dogs, inhaled budesonide suppressed eosinophil levels and the serum factor responsible for the hyperresponsiveness to acetylcholine.

- C. Nonclinical safety issues relevant to clinical use
None.

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2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-949

Review number: 1

Sequence number/date/type of submission: 000, 9/12/05/original

Information to sponsor: Yes () No ()

Sponsor and/or agent: AstraZeneca

Manufacturer for drug substance: AstraZeneca AB

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

Division name: Division of Pulmonary and Allergy and Drug Products.

HFD #: 570

Review completion date: 5/17/06

Drug:

Trade name: Pulmicort Turbuhaler M3.

Generic name: Budesonide.

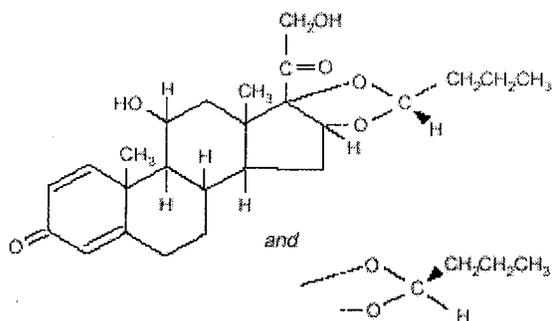
Code name: Not stated.

Chemical name: (RS)-11 β , 16 α , 17, 21-Tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17- acetyl with butyraldehyde.

CAS registry number: 51333-22-3

Molecular formula/molecular weight: C₂₅H₃₄O₆/ 450.53

Structure:



Relevant INDs/NDAs/DMFs: IND 63,762, NDA20-441.

Drug class: Glucocorticoid.

Intended clinical population: Asthmatics.

Clinical formulation: Metered dose inhalers, M3 90 and M3 180. The components are shown in the following table. The doses of lactose monohydrate, the excipient, are acceptable.

Micronized Ingredient	mcg/Inhalation	
	M3 90	M3 180
Budesonide	90	180
Lactose		

b(4)

Route of administration: Inhalation.

Maximum Daily Dose: Adults, ≥ 12 years 1440 mcg; children, ≥ 6 years, 720 mcg.

Studies reviewed within this submission: The applicant referred all preclinical studies to NDA 24-441.

Studies not reviewed within this submission: None.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: Refer to review of NDA20-441.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Refer to review of NDA20-441.

Drug activity related to proposed indication: Refer to review of NDA 20-441.

2.6.2.3 Secondary pharmacodynamics: Refer to review of NDA 20-441.

2.6.2.4 Safety pharmacology

Neurological effects: NA.

Cardiovascular effects: Refer to review of NDA 20-441.

Pulmonary effects: Refer to review of NDA 20-441.

Renal effects: Refer to review of NDA 20-441.

Gastrointestinal effects: NA.

Abuse liability: NA.

Other: Refer to review of NDA 20-441.

Pharmacodynamic drug interactions: Refer to review of NDA 20-441.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: NA.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: Refer to review NDA20-441.

2.6.4.2 Methods of Analysis: NA.

2.6.4.3 Absorption: Refer to review of NDA 20-441.

2.6.4.4 Distribution: Refer to review of NDA 20-441.

2.6.4.5 Metabolism: Refer to review NDA 20-441.

2.6.4.6 Excretion: Refer to review NDA 20-441.

2.6.4.7 Pharmacokinetic drug interactions: Refer to review of NDA 20-441.

Other Pharmacokinetic Studies: NA.

2.6.4.9 Discussion and Conclusions: Refer to review NDA 20-441.

2.6.4.10 Tables and figures to include comparative TK summary: NA.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary: Refer to review of NDA 20-441.

General toxicology: Refer to review of NDA 20-441.

Genetic toxicology: Refer to review of NDA 20-441.

Carcinogenicity: Refer to review of NDA 20-441.

Reproductive toxicology: Refer to review of NDA 20-441.

Special toxicology: Refer to review of NDA 20-441.

2.6.6.2 Single-dose toxicity: Refer to review of NDA 20-441.

2.6.6.3 Repeat-dose toxicity: Refer to review of 20-441.

2.6.6.4 Genetic toxicology: Refer to review of NDA 20-441.

2.6.6.5 Carcinogenicity: Refer to review of NDA 20-441.

2.6.6.6 Reproductive and developmental toxicology: Refer to review of NDA 20-441.

2.6.6.7 Local Tolerance: NA.

2.6.6.8 Special Toxicology Studies: Refer to review of NDA 20-441.

2.6.6.9 Discussion and Conclusions: Refer to review of NDA 20-441.

2.6.6.10 Tables and Figures: NA.

2.6.7 TOXICOLOGY TABULATED SUMMARY

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Budesonide by the inhalation route possesses typical glucocorticoid activity. From a preclinical standpoint, there are no safety or toxicity issues when administered at the recommended doses. The label is modified to conform to the Agency's standard.

Unresolved toxicology issues (if any): None.

Recommendations: Approval of NDA 21-949 with the labeling changes.

Suggested labeling:

The following labeling additions are in **bold** and deletions are in ~~strikethrough~~. Determination of the ratios is shown in the following table.

Carcinogenesis, Mutagenesis, Impairment of Fertility

b(4)

b(5)

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 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

✓ Draft Labeling (b5)

 Deliberative Process (b5)

b(5)

3

b(4)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

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Drug: **N21949 Turbohaler Budesonide**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m ²
Pediatric	6	0.18	4	0.72	20	0.036	25	0.9
Adult	>12	0.18	8	1.44	50	0.0288	37	1.0656

	route	mg/kg/d	conv. factor	mg/m ²	Dose Ratio		Rounded Dose Ratio	
					Adults	Children	Adults	Children
<u>Carcinogenicity:</u>								
rat	oral	0.025	6	0.15	0.1408	0.1667	< 1	< 1
rat	oral	0.05	6	0.3	0.2815	0.3333	< 1	< 1
mouse	oral	0.2	3	0.6	0.5631	0.6667	< 1	< 1
rat	oral	0.01	6	0.06	0.0563	0.0667	< 1	< 1
mouse			3	0	---	---	---	---
<u>Repro/Fertility:</u>								
rat	s.c.	0.02	6	0.12	0.1126	N/A	< 1	N/A
rat	s.c.	0.005	6	0.03	0.0282	N/A	< 1	N/A
rat	inhal	0.25	6	1.5	1.4077	N/A	1	N/A
extra			---	---	---	N/A	---	N/A
<u>Teratogenicity:</u>								
rabbit	s.c.	0.025	12	0.3	0.2815	N/A	< 1	N/A
rat	s.c.	0.5	6	3	2.8153	N/A	3	N/A
rat			6	0	---	N/A	---	N/A
rabbit			12	0	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
<u>Overdosage:</u>								
mouse	oral	200	3	600	563.06	666.67	560	670
mouse	inhal	100	3	300	281.53	333.33	280	330
rat	oral	100	6	600	563.06	666.67	560	670
rat	inhal	68	6	408	382.88	453.33	380	450

APPENDIX/ATTACHMENTS: REVIEW OF NDA 20-441.

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NDA 21-day Pharmacology fileability check list

NDA No.: 21-949

Date of submission: 9/12/05

Date of fileability meeting: 10/18/05

Date of checklist: 10/18/05

(1) On its face, is the pharm/tox section of the NDA organized in a manner to allow substantive review? Yes (X) No () NA ()

(2) On its face, is the pharm/tox section of the NDA legible for review?

Yes (X) No () NA ()

(3) Are final reports of all required and requested preclinical studies submitted in this NDA? NA (X). This is a change in the formulation and the delivery of an approved drug. Summaries of studies submitted were derived from INDs 31,308, 44,535, _____, and _____ and NDAs 20-233, _____ 20-746, and 20-929. However, these references were not provided in Module 4.

b(4)

	Yes	No	NA
Pharmacology	(X)	()	()
ADME	(X)	()	()
Toxicology (duration, route of administration and species specified)			
acute	(X)	()	()
subchronic and chronic studies	(X)	()	()
reproductive studies	(X)	()	()
carcinogenicity studies	(X)	()	()
mutagenicity studies	(X)	()	()
special studies	()	()	(X)
others	()	()	(X)

(4) If the formulation to be marketed is different from the formulation used in the toxicology studies, is repeating or bridging the studies necessary? Yes () No (X) NA ()

If no, state why not?

The addition of lactose to the formulation requires no additional preclinical studies.

If yes, has the applicant made an appropriate effort to repeat the studies using the to be marketed product, to bridge the studies or to explain why such repetition or bridging should not be required? Yes () No () NA ()

(5) Are the proposed preclinical labeling sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and overdosage) appropriate (including human dose multiples expressed in either mg/m² or comparative systemic exposure levels) and in accordance with 201.57? Yes (X) No (). The ratios of the animal data to the human maximum clinical dose should be modified to reflect our current practice.

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion?
Yes () No () NA (X)

(7) On its face, does the route of administration used in the pivotal toxicity studies appear to be the same as the intended clinical route? Yes (X) No () NA ()

If not, has the applicant submitted a rationale to justify the alternative route?
Yes () No () NA

(8) Has the applicant submitted a statement(s) that all of the toxicity studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? Yes () No () NA (X)

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)? Yes () No () NA (X)

(10) Are there any outstanding preclinical issues? Yes () No (X)

If yes, identify those below

(11) From a preclinical perspective, is this NDA fileable? Yes (X) No ()

If no, state below why it is not.

Should any additional information/data be requested? Yes (X) No () In Module 4, references to the submitted summaries of the Non-Clinical Study Reports derived from the INDs and NDAs should be provided.

NDA 45-day Planning Timeline

NDA No.: 21-0949

Date of 45-day planning meeting: 10/18/05

Date of planning timeline: 10/18/05

User Fee Due Date: NA

Final review completion date: 4/1/06

	Milestone Dates
Pharmacology and ADME	NA
Toxicology	NA
General toxicity studies	
Carcinogenicity studies and mutagenicity studies	
a. Statistical consult request for CA studies	
b. Submission of CA studies for CAC concurrence	
Reproductive studies	
Special studies and Others	
Labeling	4/1/06

Reviewing Pharmacologist/Toxicologist: Lawrence F. Sancilio, Ph.D.

Team Leader: S. Joseph Sun, Ph.D.

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/s/

Lawrence Sancilio
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Joseph Sun
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I concur.

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