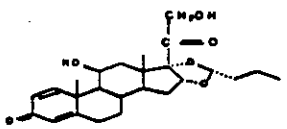
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-746

PHARMACOLOGY REVIEW(S)

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original, Review No. 3

NDA No.	20-746
Dates and contents of submission:	6-MAY-98: 6-month inhalation toxicity study of polysorbate 80 and potassium sorbate in rats
Information to be conveyed to sponsor:	Yes ( ), No (X).
Reviewer:	Luqi Pei, Ph.D. (HFD-570)
Date of review completed:	August 14, 1998
Sponsor:	Astra USA, Westborough, MA.
Drug: *Brand Name:*	Rhinocort AQ Nasal Spray
Generic Name:	Budesonide
Chemical Name:	16α,17α-butylidenedioxy-pregna-1,4-diene-11β,21-diol-3,20-dione
Structure:	
CAS Registry number:	51333-22-3
Formula and Molecular Weight:	$C_{25}H_{34}O_6$; MW = 430.5
Class:	Corticosteroid
Indication:	Seasonal or perennial allergic rhinitis in adults and children 6 years and older
Route of Administration:	Nasal Spray
Proposed Clinical Dose:	256 µg/day, corresponding to a daily dose of 5.1 µg/kg in adults and 12.8 µg/kg/day in 6 year old children.

Related INDs and NDAs

NDA 20441, IND [redacted]	Pulmicort Turbuhaler
NDA 20-233, IND [redacted]	Rhinocort (budesonide) Nasal Inhaler
IND [redacted]	[redacted]
IND	
IND	
IND	

Previous Reviews:

NDA [redacted]
NDA 20-746, 11-04-96, 5-30-97, Luqi Pei, Ph.D.
NDA 20-441, 6-11-96, Lawrence F. Sancilio, Ph.D. and Luqi Pei, Ph.D.
NDA 20-233, 7-23-93, Conrad H. Chen, Ph.D.
NDA [redacted]

Documents review in this NDA submission:

General toxicity study of budesonide nebulizing suspension and polysorbate 80 and potassium sorbate given to young rats by the inhalation route for 6 months. Plasma concentration study. Vol. 1, page 1, submitted on 5-6-98.

Background:

During the evaluation of the Rhinocort AQ Nasal Spray application, it was agreed that Astra, as a phase 4 commitment, would conduct a 6 month inhalation toxicity study in rats to evaluate nasal toxicity of two inactive ingredients: polysorbate 80 and potassium sorbate. The Agency would review the data for safety evaluation of the inactive ingredients once the study results became available. (See meeting minutes of the pre-NDA meeting on December 6, 1998.) Astra has recently completed the study and submitted the information to fulfill the previous requirement (via request on May 5, 1998).

The study protocol was reviewed previously by the Division. The divisional comments were conveyed to Astra via telephone conversation on 14-Jan-97. Most comments were incorporated into the study design: adding a low dose group for the excipient, prolonging the exposure duration, and raising the concentrations of polysorbate 80 and potassium sorbate. Astra doubled the concentration of polysorbate 80 and raised the concentration of potassium sorbate from the proposed [redacted] These concentrations were believed to be the maximum technical achievable concentrations.

Review:

This study has been reviewed previously by [redacted] under NDA No. [redacted] polysorbate 80 [redacted] that is also present in Rhinocort AQ nasal spray [redacted] Rhinocort AQ nasal spray also contains [redacted] potassium sorbate. More information about Rhinocort AQ formulation can be found in previous review by L. Pei (May 30, 1997).

In the 6-month inhalation study, 25-day-old Wistar rats (20/sex/dose) were exposed nose-only to the mixture of polysorbate 80 and potassium sorbate for a daily duration of 60 minutes (low dose) to 240 minutes (high dose). The estimated animal exposures of the excipients are listed in Table 1.

Table 1. Dose estimates of excipients in rats

Chemical Group	Potassium sorbate		Polysorbate 80	
	Low dose	High dose	Low dose	High dose
Mean testing substance concentration (µg/L)	10.4 ± 2.1	10.0 ± 2.6		
Exposure duration (min)	60-84	180-252	60-84	180-252
Mean particle size (µm)	2.01	2.08	2.01	2.08
Theoretical exposure				
Inhaled dose (µg/kg)[1]	498	1,446	332	964
Total body exposure (µg/kg)[2]	210	658	93.3	292
Lung deposition (µg/kg)[3]	57.7	182	25.6	80.9
Nasal deposition (µg/kg)[4]	100	289	67	193

1. Calculated by mean aerosol concentration x duration of exposure x respiratory volume (RMV) / body weight (BW). Where RMV = $BW(g)^{0.66}$ x 4.19.
2. Derived by the inhaled dose x the total collection efficiency. The total collection efficiency for the low and high dose groups were 0.42 and 0.45. (ref: *Raabe OG et al, Deposition of inhaled monodisperse aerosols in small rodents. In Walton WH, ed. Inhaled particles IV. New York: Pergmon Press, 1977:3-21*).
3. Based on lung deposition efficiency of 0.12 and 0.13 for the low and high dose groups.
4. Based on nasal deposition efficiency of 0.2 for both groups.

These two excipients did not induce any local or systemic toxic responses (including the respiratory system) at the highest dose tested [redacted]. Nor were abnormalities found in the rat nasal cavity. Two additional groups were given clinical formulations of budesonide nebulizing solution for reference. These animals showed the typical steroid effects and were already discussed in the [redacted] review. Additional discussions in this review are not necessary. This review addresses the safety of potassium sorbate and polysorbate 80 in the nasal cavity only.

The safety evaluation of the excipients is based on the surface area of the nasal cavity as it may a better predictor of local exposure. The theoretical nasal exposures to the excipients (high dose) and its relationship to human exposure are summarized in Table 2. The nasal chemical concentrations in the high dose rats were 5 – 15 folds higher than the expected clinical exposure in humans and no abnormalities were observed in these animals.

Table 2. Nasal exposure of the excipients in rats and humans

	Potassium sorbate		Polysorbete 80	
	Rat (adult)	Child (6 yr.)	Rat (adult)	Child (6 yr.)
Nasal surface area (cm^2)	10[1,3]	150[2]	10	150
Exposure				
µg/individual	72.3	240[4]	48.3	50
$\mu g/cm^2$	7.2	1.6	4.8	0.3
Dose ratio (rat/child)	-	4.5	-	14.5

1. Estimated for a 250-gram rat (ref: *Allometrac plot*. Gehr et al, J Resp Physiol, 1981;44:61).
2. Extrapolated for 6 year-old child, (ref: Patra et al, *The Anatomical Resord*, 1986;215:42-50.
3. Scheider JP, *In Nasal tumors in animals and man. Vol III Exprimental nasal carcinogenesis*. Eds.: Reznik ann Stinson, CRC Press, 1983.
4. Assuming 100% deposition efficiency in the nasal cavity.

Conclusion:

Toxicity of potassium sorbate and polysorbate 80, the two expipients in Rhioncort AQ nasal spray, has been tested in rats as suggested by the Agency previously (meeting minutes of October 2, 1996 and teleconference of January 14, 1997). They were found to be non-toxic both locally and systemically after 6 months of inhalation exposure at dose levels of 5 - 15 fold higher than the expected clinical exposure, based on the surface area. Therefore, safety of these excipients in this drug product has been established and the issue of excipients in the DNA application is considered as resolved; no further action is needed in this NDA with regard to the non-clinical toxicity testing of its excipients.

Recommendation:

None.

/S/
/S/ 8/14/98
Pharmacologist

Review completed on August 10, 1998.
Revised by Dr. Hilary Sheevers on August 12, 1998

cc: HFD-570/Division File
HFD-570/ Pei/ Anthracite/ Sheevers/ Himmel /Trout

/S/
8/14/98

Trout

OCT 8 1997

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original, Review No. 3

NDA No. 20-746

Dates and contents of Submission:

Information to be conveyed to Sponsor: Yes (X), No ( ).

Reviewer: Luqi Pei, Ph.D. (HFD-570)
Lawrence Sancilio, Ph.D.

Date of Review Completed: October 7, 1997

Sponsor: Astra USA, Westborough, MA.

Drug Name: *Brand Name:* Rhinocort AQ Nasal Spray
Generic Name: Budesonide

Class: Corticosteroid

Indication: Seasonal or perennial allergic rhinitis in adults and children of 6 year and older

Route of Administration: Nasal Spray

Proposed Clinical Dose: 256 µg/day (i.e., 4 actuations once a day). This is equivalent to 5.1 µg/kg/day in adults (body weight of 50 kg) and 12.8 µg/kg/day in 6 year old (body weight of 20 kg).

Related INDs and NDAs:

NDA 20441 Pulmicort
NDA 20-233 Rhinocort (budesonide) Nasal Inhaler
IND
IND
IND
IND
IND

Previous Review:

NDA 20-746, 05-30-97, Luqi Pei, Ph.D., Original review
NDA 20-746, 11-04-96, Luqi Pei, Ph.D., A review of inactive ingredients
NDA 20-441, 6-11-96, Lawrence F. Sancilio, Ph.D. and Luqi Pei, Ph.D.
NDA 20-233, 7-23-93, Conrad H. Chen, Ph.D.
NDA [redacted]

Labeling Review Amendment:

Labeling review for this submission was conducted previously (Pharmacologist/ toxicologist's review of Luqi Pei on May 30, 1997); however, recent divisional policies in standardizing labeling warrant substantial changes to the previous review. To keep consistency between the drug formulations, the recently approved labeling for Nasacort® AQ nasal spray (approval date of 9/25/97) was used as a template.

The division recently (June 24, 1997) approved another budesonide product - Pulmocort® turbuhaler (NDA 20-441). Preclinical sections of the labeling for the pulmocort® may need updating in order to keep labeling consistency for drugs with the same active ingredient and from the same sponsor. The following is the revised and suggested the preclinical sections of the labeling of the budesonide products, with the exception of dose ratios:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a two-year study in Sprague-Dawley rats, budesinode caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 µg/kg (approximately [redacted] the maximum recommended daily intranasal dose in adults and children on a µg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 µg/kg (approximately [redacted] to the maximum recommended daily intranasal dose in adults and children on a µg/m^2 basis, respectively). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 µg/kg (approximately [redacted] the maximum recommended daily intranasal dose in adults and children on a µg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 µg/kg (approximately [redacted] the maximum recommended daily intranasal dose in adults and children on a µg/m^2 basis). The concurrent reference steroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 µg/kg (approximately [redacted] times the maximum recommended daily intranasal dose in adults and children on a µg/m^2 basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames Salmonella/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

In rats, budesonide caused a decrease in prenatal viability and viability of the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 µg/kg and above (the maximum recommended daily intranasal dose in adults on a µg/m^2 basis). No such effects were noted at 5 µg/kg (the maximum recommended daily intranasal dose in adults on a µg/m^2 basis).

PREGNANCY: Teratogenic Effects: Pregnancy Category C: Budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights and skeletal abnormalities at respective subcutaneous doses 25 and 500 µg/kg in rabbits and rats (approximately times the maximum recommended daily intranasal dose in adults on a µg/m^2 basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 µg/kg (approximately 8 times the maximum human daily intranasal dose in adults on a µg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from than humans. In addition, because there is a natural increase in production during pregnancy, most women will require a lower exogenous dose and many will not need treatment during pregnancy.

/S/ 10/8/97
Lawrence Sancilio, Ph.D.
Pharmacologist/Toxicologist

/S/ 10/8/97
Luqi Pei, Ph.D.
Pharmacologist/Toxicologist

cc: HFD-570/Division File
HFD-570/ Pei/ Anthracite/ Sheevers/ Himmel /Trout /Sancilio

/S/ 10/8/97

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DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original, Review No. 2

NDA No. 20-746

Dates and contents of Submission:

96-06-29	Original submission
96-11-01	Supplement, correspondence to inquiry of inactive ingredients
96-11-21	Supplement, impurity information
96-12-03	Supplement, 2 & 4 week inhalation toxicity studies in rats
97-04-17	Supplement, microscopic findings of the 4 wk inhalation study in rats

Information to be conveyed to Sponsor: Yes (X), No ( ).

Reviewer: Luqi Pei, Ph.D. (HFD-570)

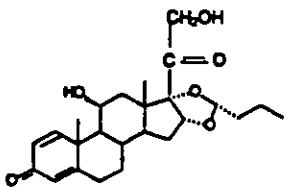
Date of Review Completed: May 30, 1997

Sponsor: Astra USA, Westborough, MA.

Drug Name: *Brand Name:* Rhinocort AQ Nasal Spray
Generic Name: Budesonide

Chemical Name: 16α,17α-butylidenedioxy pregna-1,4-diene-11ß,21 -diol-3,20-dione

Structure:



Formula and Molecular Weight: 430.5

Class: Corticosteroid

Indication: Seasonal or perennial allergic rhinitis in adults and children of 6 year and older

Route of Administration: Nasal Spray

Proposed Clinical Dose: 256 µg/day (i.e., 4 actuations once a day). This is equivalent to 5.1 µg/kg/day in adults (body weight of 50 kg) and 12.8 µg/kg/day in 6 year old (body weight of 20 kg).

Formulation:

Ingredient	64 µg strength mg/actuation	64 µg strength Concentrat'n (%)	32 µg strength mg/actuation	32 µg strength Concentrat'n (%)	Standard
Budesonide, micronized					
Cellulose/ methyalcarboxymethyl c.					NF
Dextrose					USP
Polysorbate 80					NF
Edetate disodium					USP
Potassium sorbate					NF
Hydrochloride acid					NF
Water					USP

Related INDs and NDAs:

NDA 20441 Pulmicort

NDA 20-233 Rhinocort (budesonide) Nasal Inhaler

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IND

Previous Review:

NDA 20-746, 11-04-96, Luqi Pei, Ph.D., A review of inactive ingredients

NDA 20-441, 6-11-96, Lawrence F. Sancilio, Ph.D. and Luqi Pei, Ph.D. (Appendix A)

NDA 20-233, 7-23-93, Conrad H. Chen, Ph.D. (Appendix B)

NDA

Documents review in this NDA submission:

Pharmacology

Inhibition of Allergen-induced plasma exudation in rat ileum by oral budesonide and prednisolone. Study No. 850-RD-375. Vol 1.8, p 11. Submitted on 6/29/96.

Antiinflammatory effect of oral budesonide in oxazolone-induced colitis in rats. Study No. 850-RD-033. Vol 1.8, p 25. Submitted on 6/29/96.

Effect of inhaled budesonide on airway/lung hyper-responsiveness and inflammatory cell responses in oleic acid challenged dyspnea bred rats. Study No. 850-RD-0377. Vol 1.8, p 91. Submitted on 6/29/96.

Decrease in plasma cortisol levels by oral budesonide in guinea pigs. Study No. 850-RD-0379. Vol 1.8, p 119. Submitted on 6/29/96.

Lack of antiexudative effect of budesonide in a rat ileal mucosa model. Study No. 850-RD-0380. Vol 1.8, p 128. Submitted on 6/29/96.

A review of preclinical ocular effects of budesonide. Study No. 850-RD-0139. Vol 1.8, p 158. Submitted on 6/29/96.

Pharmacokinetics

Pharmacokinetics of oral and IV budesonide in beagle dogs. Study No. 850-RD-0376. Vol 1.8, p 59. Submitted on 6/29/96.

Toxicology

14-Day inhalation dose ranging study in rats, Study No. T3260. Vol. 6.2, p 1. Submitted 12/3/96.

4-week inhalation toxicity study with 1-month recovery period in rats. T3289. Vol. 6.3, p 1. Submitted on 12/3/96.

Environmental Assessment

Environmental assessment report. Vol. 1.6, p 1. Submitted on 6/29/96.

Document not reviewed in this review:

Brattsand R et al. (1987). Development of glucocorticosteroids with lung selectivity. In: Advances in the use of inhaled steroids. Ed. Ellul-Micheal R et al. *Excerpta Medica*, Amsterdam. P 60 - 85. This document is not needed to evaluate the safety of budesonide.

Background:

Rhinocort Aqua nasal spray is a reformulation product of Rhinocort Nasal Inhaler that was approved for marketing on February 14, 1994 (NDA 20233). Budesonide is the active ingredient of the Rhinocort nasal inhaler. The proposed dosage of budesonide of Rhinocort AQ nasal spray is the same as that of the Rhinocort nasal inhaler. Pulmicort Turbuhaler (NDA 20441) is another product that contains budesonide as the active ingredient. Preclinical pharmacology and toxicology of budesonide has been reviewed as described in the Previous Review section. This review covers only several pharmacology and toxicology studies

submitted in support of this NDA and an evaluation of the newly proposed product.

Review:

Pharmacology:

Budesonide (PO) reduced allergen-induced plasma exudation at dose as low as 0.1 mg/kg in a rat ileal model (850-RD-375). The drug was 30 times more potent than prednisolone on a mg/kg basis. Budesonide (PO), however, had no efficacy against acetic acid-induced colitis in a guinea pig model (850-RD-0380). Prophylactic treatment (PO or intrarectal) with budesonide inhibited infiltration of inflammatory cells into the lumen in an oxazolone-induced colitis in rats (850-RD-033). Inflammation was measured by myeloperoxidase activity and colon weight. Inhaled budesonide inhibited airway/lung hyper-responsiveness and inflammatory cell responses in oleic acid challenged dyspnea bred rats (850-RD-0377). Oral budesonide decreased plasma cortisol levels in guinea pigs (850-RD-0379).

Pharmacokinetics

Plasma concentrations of budesonide after 5 minutes of continuous intravenous infusion or inhalation exposure were determined in female beagle dogs (850-RD-0376). Samples were analyzed by a combination of [redacted] The lower limit of quantitation was [redacted] Immediately after IV infusion, plasma budesonide concentration was approximately 34 nmol/l. The MRT, T1/2, CL, Vd, and Vss were 1.4 h, 2.2 h, 2.2 l/h/kg, 6.9 l/kg, and 3.2 l/kg, respectively. Budesonide was rapidly absorbed after inhalation administration and its pharmacokinetic profiles were similar to the IV administration. Bioavailability of inhaled budesonide was 58.6%.

Toxicology

1. 14-Day inhalation dose ranging study in rats, Study No. T3260. Vol. 6.2, p 1. Submitted 12/3/96.

Testing lab:	Laboratory of Safety Assessment, AB Astra, Sweden
Study number:	95078
Study dates:	8/15/95 - 8/31/95, Report date - 5/14/96
GLP:	Yes
Dose:	0 (C), 0.05 (L), 0.41 (M), 4.6 (H) μg/kg
Batch No.	514-01, 1617-1 (5.0% Budesonide + 95% lactose)

Methods:

Three groups of Wistar rats (10/sex/dose) were exposed to 0.15, 0.62 and 6.7 μg budesonide/L air in a nose-only exposure chamber for 5 - 10 minutes/day for 14 days. The control group received lactose (1.4 mg/L air) only. The respective estimated doses of budesonide

in the treated groups were 0.54, 4.4 and 49 μg/kg/day for inhaled and 0.2, 1.6, and 17 μg/kg/day for total body burden and 0.05, 0.41, and 4.6 μg/kg for the respiratory tract and lung deposition. The estimated MMAD was [redacted] μm. These animal were sacrificed on day 15 for necropsy. No microscopic examinations were conducted on animals of scheduled sacrifice.

Results:

Mortality: Two HD male rats died during the study. The cause of death was not established.

Clinical signs (daily): No treatment-related effects were observed.

Body weight (weekly): The HD group showed decreased body weight gain: (24% and 50% for the male and females at week 2 respectively).

Food consumption (weekly): Food consumption decreased as a function of dose in the males, but only the decrease (12%) in the HD group at week 1 was statistically significant.

Clinical chemistry (Days 14):

Hematology: Slight hemo-concentration was seen in the HD group. This was indicated by slight but statistically significant increases (< 10%) in means of erythrocyte numbers, hemoglobin concentrations, and hematocrit. These changes were within normal reference range of the laboratory.

Blood chemistry: Slight increases in plasma glucose levels (< 34%) and urea levels (< 15%) were seen in the low and mid dose males, but not in the other groups. All these numbers were within the normal reference range of the laboratory.

Ophthalmology: No treatment-related effects were observed.

Organ weights: Dose-dependent decreases in thymus and liver weight (both absolute and relative) were evident in all male groups and the HD females. The severity of decreases in the absolute thymus weight were between 20 - 30%. A fourteen percent decrease in liver weight was seen in the high dose males.

Pathology:

Necropsy: No treatment related effects were observed.

Histopathology: Microscopic examinations were performed on the 2 pre-terminally dead rats only. Both animals showed interstitial pneumonia. It is unclear whether these deaths were treatment-related.

Conclusion: Inhalation exposure of budesonide for up to 0.41 μg/kg/day did not produce significant toxicological effect in rats. At a higher dose level (4.6 μg/kg/day), decreases in body weight gain, in thymus weight and serum glucose levels, and an increase in liver weight were observed. These observations are typically associated with repeated administration of corticosteroids. In addition, two male rats died of pneumonia during the experiment, however no

histological changes of the target organs (thymus and liver etc.) were found. Histological examinations was not conducted for the remaining animals. Interstitial pneumonia is an infectious disease and treatment-related increases in incidences of infections is considered an indication of immunotoxicity (the draft [redacted] Furthermore, glucocorticosteroid is known to cause immunosuppression. Therefore, the mortality is at least indirectly attributed to the budesonide treatment. NOAEL values appeared to be 0.05 µg/kg/day for the males and 0.41 µg/kg/day for the females.

2. 4-week inhalation toxicity study with 1-month recovery period in rats. Study No. T3289. Vol. 6.3, p 1. Submitted on 12/3/96.

Testing lab:	Laboratory of Safety Assessment, AB Astra, Sweden
Study number:	95078
Study dates:	9/27/95 - 11/23/95, Report date - 6/18/96
GLP:	Yes
Dose:	0 (C), 0.03 (L), 0.31 (M), 4.1 (H) µg/kg
Batch No.	514-01, 1617-1 (5.0% Budesonide + 95% lactose)

Methods:

Three groups of Wistar rats (10/sex/dose) were exposed to 0.16, 0.70 and 6.1 µg budesonide/L air in a nose-only exposure chamber for 2.5 - 10 minutes/day for 4 weeks. The control group received lactose (1.4 mg/L air) only. The respective estimated doses of budesonide in the treated groups were 0.28, 3.3 and 43 µg/kg/day for inhaled and 0.12, 1.1, 16 µg/kg/day for body burden and 0.03, 0.31, and 4.1 µg/kg for the respiratory tract and lung deposition. The estimated MMAD was [redacted] µm. Animals (5/sex/dose) were sacrificed on day 29 and 57 for necropsy and histological examinations. Three more groups of animals (control, MD and HD) were used for the reversibility of changes after a recovery period of 4 weeks.

Results:

Mortality: None.

Clinical signs (daily): No apparent treatment-related effects were observed.

Body weight (weekly): The HD groups (both the main study and the satellite animals) showed decreases in body weight gain starting from week 1. By week 4, the decreases in body weight gain were 17% and 50% for the male and females, respectively. The body weight gain returned to normal shortly (2 weeks in the females) after discontinuation of the treatment.

Food consumption (weekly): No apparent treatment-related effects were observed.

Ophthalmology: No apparent treatment-related effects were observed.

Clinical chemistry (Days 30 and 60): No apparent treatment-related effects were observed in hematology, blood chemistry, and urinalysis. Slight (≤ 10%) and sporadic changes were not considered toxicologically significant.

Organ weights: Decreases in mean thymus weight (both absolute and relative) were

observed in HD groups (↓ 22 - 31% in relative mean thymus weight). Thymus weight, however, returned to normal after a 4-week recovery period.

Pathology:

Necropsy: No treatment related effects were observed.

Histopathology (control and high dose only): The summary table of the microscopic examinations was missing from the pathology report in the original submission. The sponsor stated that there were no microscopic findings associated with budesonide treatment. An evaluation of the data submitted by the sponsor (Supplement 4/17/97) upon request (April 2, 1997) confirmed the previous conclusion.

Plasma drug levels (from satellite animals on days 0, 6, and 27): The limit of quantitation was [redacted] nmol/l when 1.0 ml plasma was used. AUC_{0-t} values are listed in Table 1 (nmol/l.h):

Table 1. Plasma budesonide levels in a 4-week inhalation study in rats (T3289)

		Male			Female		
		Dose * (µg/kg)	AUC total (nmol.h/L)	Cmax (nmol/L)	Dose * (µg/kg)	AUC total (nmol.h/L)	Cmax (nmol/L)
Mid dose	Day 0	2.9	1.22	1.83	3.2	1.37	1.74
	Day 6	3.4	-	-	3.7	-	1.79
	Day 27	3.6	1.29	2.34	4.1	1.79	2.06
High dose	Day 0	29	10.9	16.0	31	21.5	10.4
	Day 6	41	-	-	47	-	16.4
	Day 27	35	12.9	19.0	40	16.1	20.5

* Inhaled doses.

Conclusion: Inhalation exposure of budesonide at doses of up to 4.1 µg/kg/day (lung deposition, high dose) for 4 weeks produced moderate decreases in body weight gain and thymus weight in rats. These parameters, however, returned to normal upon cessation of the drug. No treatment-related effects were observed al dose levels of or less than 0.31 µg/kg/day. The NOAEL for the 4-week inhalation exposure was 0.31 µg/kg/day.

Summary.

Toxicity of inhalational budesonide was evaluated in rats for up to 4 weeks. A 2-week study indicated that repeated administration of high dose of the drug (lung and tracheal dose of 4.6 µg/kg/day) could result in mortalities. Two of the 10 animals died because of interstitial pneumonia. Other animals in the group showed slight decreases in thymus weight and body weight gain. No apparent abnormalities were observed at lower doses (≤ 0.31 µg/kg/day).

In a 4-week inhalation study, rats were exposed to budesonide at doses of 0.03, 0.3 and 4.1 µg/kg/day (lung deposition). The high dose produced decreases in body weight gain and thymus weight. These parameters, however, returned to normal upon cessation of the drug. No

treatment-related effects were observed at dose equal to or less than 0.31 µg/kg/day. The NOAEL was 0.31 µg/kg/day.

OVERALL SUMMARY AND EVALUATION

Budesonide has been approved for human use in the US and 31 other countries since 1982. The preclinical pharmacological and toxicological profiles of budesonide has been well established in studies supporting the intranasal and inhalation administration. Rhinocort nasal inhaler is an approved budesonide nasal product (NDA 20233). This product is indicated for the management of symptoms of seasonal or perennial allergic rhinitis in adults and children and non-allergic perennial rhinitis in adults. Another budesonide inhalation product, Pulmicort turbuhaler (NDA 20441), is under review process in the division. Pulmicort is indicated for treatment of bronchial asthma and is likely to be approved. The preclinical pharmacology and toxicology data of budesonide have been previously reviewed in respective NDA applications by Conrad. H. Chen, Ph.D. (7-26-1993), [redacted], and Lawrence Sancilio, Ph.D. and Luqi Pei, Ph.D. (6-11-1996). The following is a brief summary of these reviews.

Pharmacodynamics: Budesonide is a glucocorticoid receptor agonist. The receptor affinity of budesonide is 8, 17, and 200 times of dexamethasone, prednisolone and hydrocortisone, respectively. Like other glucocorticosteroids, budesonide possesses potent local anti-inflammatory activity. This is illustrated its ability to inhibit: 1) allergen-induced plasma exudation, 2) infiltration of inflammatory cells, and 3) airway/lung hyper-responsiveness and inflammatory cell responses. The precise mechanism on anti-inflammation of these drugs is not known. Glucocorticosteroids have been shown to have a wide range of inhibitory activities against multiple cells and mediators involved in allergic and non-allergic inflammation.

Pharmacokinetics: Absorption of budesonide after oral and inhalation administration was rapid. Oral bioavailability of budesonide is lowest in monkeys (2%) and highest in mice (35%). Humans (10 %) and dogs (18%) are in between. Inhalational bioavailability of budesonide was three times higher than the oral formulations in both dogs and humans for equivalent doses. Tissue concentration of budesonide after inhalation/intratracheal administration is the highest in the lung. The lung is followed by the liver, heart, spleen and brain. Budesonide can probably be stored as pharmacologically inactive fatty acid conjugates intracellularly in the lung. The conjugated drug can be reactivated upon the cleavage of a fatty acid, thus prolonging the duration of drug action. Budesonide was mainly metabolized in the liver by the cytochrome P450 enzyme 3A (CYP3A) family to 16α-hydroxyprednisolone in both rats and humans. Half-lives of budesonide ranged from 2 - 4 hours. Budesonide was mainly excreted through bile into the feces. The percentage of protein binding in the plasma was similar (85% - 92%) across species including humans.

General toxicity: Acute, subchronic and chronic toxicity of budesonide has been evaluated in mice, rats, dogs and monkeys by various routes of administration. The respective subcutaneous and oral LD50 values were 35 mg/kg and > 100 mg/kg in mice and 20 mg/kg and > 400 mg/kg in rats. Toxicity profiles of budesonide after chronic exposure were typical of glucocorticosteroids. These include atrophy of the thymus, adrenals and lymph nodes, gastric ulcerations, decreases in white blood cell counts, depress of the HPA axis, increased liver glycogen, GI hemorrhage and obesity. Inhalation toxicity studies for duration of up to one year in dogs and 3 months in rats failed to induce any abnormal histological changes in the respiratory system. Ironically, a one-year rat inhalation study showed slight pulmonary inflammation (perivascular lymphocyte infiltration, accumulation of alveolar macrophages, and increased mucus production of the trachea). Significance of this finding is not known.

Genotoxicity: Budesonide was not genotoxic in a battery of 6 assays: the Ames test, mouse lymphoma cell assay, *in vitro* human lymphocyte chromosomal aberration assay, mouse bone marrow micronucleus assay, Drosophila sex-linked recessive lethal mutation assay, and the unscheduled DNA synthesis assay.

Carcinogenicity: Carcinogenicity of budesonide was evaluated in rat and mouse bio-assays using oral (drinking water) administration. A 2-year study in Sprague-Dawley rats showed that budesonide at 50 μg/kg/day (300 $\mu g/m^2$/day) induced a statistically significant increase in the incidence of gliomas in the males. Females and the lower dose males (10 and 25 μg/kg/day) did not show any induced tumorigenic effect. The finding of male gliomas was not confirmed in a repeat study at the same dose (50 μg/kg/day and male only). However, an increase in the incidence of hepatocellular tumors was observed. The hepatocarcinoma was also observed in the concurrent reference treatments (prednisolone at 400 μg/kg/day and triamcinolone at 15 μg/kg/day). A third study in male Fisher-344 rats at the same dose level did not demonstrate increased incidences of either gliomas or the hepatocarcinomas. Budesonide was not carcinogenic in mice at doses up to 200 $\mu g/m^2$/day when administered in drinking water for 91 weeks (600 $\mu g/m^2$/day).

Reproductive toxicity: Budesonide, given subcutaneously at 20 and 80 μg/kg/day, decreased pre- and post-natal viability of the offspring. Subcutaneous doses of greater than 5 and 100 μg/kg/day of budesonide was also teratogenic and embryocidal in rabbits and rats. Budesonide at 25 μg/kg/day and 500 μg/kg/day induced fetal loss, decreased pup weights, and skeletal abnormalities in rats. Budesonide also slightly increased gestation period at 80 μg/kg/day in rats.

Special toxicity: Budesonide was not an irritant to the nasal cavity (dogs), nor to the eye (rabbits) and skin (rabbits and guinea pigs). Neither did the drug produce delayed hypersensitivity (guinea pigs).

Inactive ingredients: Two inactive ingredients (potassium sorbate and polysorbate 80) are present in the final formulation. A review of the available information indicates that safe use of the 2 compounds by inhalation administration is not supported by preclinical data. (Dr. Pei's

review on July 27, 1996). The sponsor was asked to conduct a 6 month inhalation study in rats as a phase 4 commitment (Meeting minutes of December 6, 1996). The recommendation of approval, however, will not depend on the completion and the results of the mentioned study, but the study should be conducted as soon as possible. Safety of these inactive ingredients will be re-evaluated when the study results are available.

Impurities: [redacted] is identified as a budesonide degradation product in Rhinocort AQ nasal spray. Concentration of [redacted] are [redacted] for the 64 μg strength and 32 μg strength, respectively. The amount of the impurity per actuation, however, is the same (0.64 μg/actuation, supplement of 11-21-96). The estimated maximal total daily dose of this impurity at the current formulation is [redacted] μg/person/day. Dr. Ng (Chemist Reviewer) indicated that CMC review requires the sponsor to lower the level of [redacted] to less than [redacted] for the 64 μg strength. The current draft guidelines on impurities indicate a qualification threshold of 1% (Federal Register, Mar 18, 1996). Therefore, the level of [redacted] is considered as acceptable. Furthermore, structural analysis of budesonide and other steroids suggests that [redacted] likely be a pro-drug of budesonide as 17-hydroxypregesterone is to cortisone (Fig. 1). Therefore, no significantly additional toxicity is expected by presence of minute amount of the impurity. This further increases our comfort level about the safety of the [redacted] Because the 32 μg strength contains the same amount of [redacted] as the 64 μg strength does, and the impurity level in the 32 μg strength is also considered as acceptable. Thus, the levels of impurities do not impose significant safety concern from preclinical point of view.

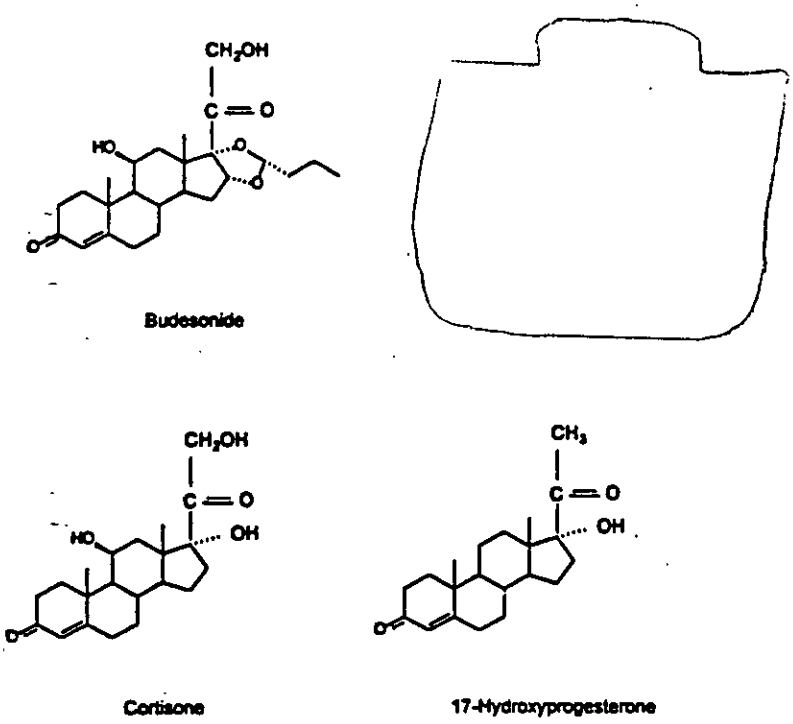


Fig 1. Structure of budesonide and other steroids.

Environmental assessment: See Environmental Assessment Review.

Recommendation

This NDA is approvable from the preclinical standpoint, based on the extensive characterization of the drug in support of this (NDA 20746) and other applications (NDA 20233 and 20441). In addition, the reformulation of the budesonide products did not significantly modify the toxicity profile of the drug (NDA 20441). However, safety of the inactive ingredients (polysorbate 80 and potassium sorbate) should be re-evaluated upon completion of the 6-month inhalation toxicity study in rats.

Labeling Review

The previously approved labeling of budesonide product (Rhinocort® Nasal Inhaler) is silent on the pediatric population. This review addresses both the adult and pediatric populations because this application is for adults and children of 6 years or older. Calculation of safety margins between preclinical doses in animal carcinogenicity studies and the clinical dose are summarized in Table 2. Daily doses based on surface area in all species are obtained by multiplying the µg/kg/day dose by a conversion factor. A human body weight of 50 kg and 20 kg is used for an adult and a 6 year-old child, respectively. It is clear that pediatrics are exposed to the drug at a higher dose (70%) than the adults. Safety margins of the carcinogenesis of the labeling section will be based on daily doses of 190 and 320 µg/m^2/day for the adult and pediatrics, respectively, whereas safety margins of the fertility and pregnancy section is based on the adult dose only (190 µg/m^2). Exposure based on body surface area was used because of the lack of toxicokinetic data in the animal carcinogenicity studies.

Table 2. Safety margins between animal carcinogenicity data and human therapeutic use

Species	Route	Dose µg/kg/day	Dose µg/m^2/day*	Safety margin (on µg/m^2) **
Human				
Adult	Nasal	5.1	189	-
Child	Nasal	12.8	320	-
Rat				
Sprague-Dawley	Drinking water	50	300	0.94 - 1.7
Fischer 344	"	50	300	
Mouse	Drinking water	200	600	1.9 - 3.2

* These doses (µg/m^2) are derived by multiplying the µg/kg dose with a conversion factor of 37, 25, 6 and 3 for adult human, child, rat and mice respectively.
** The smaller number is for pediatric population whereas the larger is for the adult population.

The following is the proposed revised preclinical labeling for carcinogenesis,

mutagenesis and impairment of fertility section for budesonide. Detailed editing is attached (see page 14) for convenience. The underline is the proposed addition while the strike out is the proposed deletion of the sponsor's proposed labeling. This editing is primarily three folds: 1) move the positive carcinogenicity findings (rat) ahead of the negative findings, and 2) standardize the labeling with current divisional language. 3) add the pediatric population in the carcinogenesis section.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

six different test systems; Ames Salmonella/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Drafted labeling editing.

The underline is the proposed addition of the sponsor's proposed labeling of the carcinogenesis section while the strike out is the proposed deletion. This editing is primarily two fold: 1) Move the positive carcinogenicity findings (rat) ahead of the negative findings, and 2) Standardize the labeling with current divisional language. 3) Add the pediatric population in the carcinogenesis labeling section.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

There was no evidence of a carcinogenic effect when budesonide was administered orally for 91 weeks to mice at doses up to 200 µg/kg/day (approximately 3 the maximum adult and pediatric human daily inhalation dose on µg/m^2 basis).

six different test systems; Ames Salmonella/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in Drosophila melanogaster, and DNA repair analysis in rat hepatocyte culture.

PREGNANCY: Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from than humans. In addition, because there is a natural increase in production during pregnancy, most women will require a lower exogenous dose and many will not need treatment during pregnancy.

No changes are recommended for the paragraph start with "Experience with oral ...).

/S/ 6/2/97

Luqi Pei, Ph.D.
Pharmacologist/Toxicologist

Review completed on April 10, 1997
Revised by Dr. Hilary Sheevers on 4-24-97, 4-28-97 and 5-29-97.

cc: HFD-570/Division File
HFD-570/ Pei/ Anthracite/ Sheevers/ Himmel /Trout

/S/ 6/2/97

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Pharmacological Review of Environmental Assessment

NDA No. 20746, Serial No. 1

Date of Submission: 6-06-29 Original submission

Information to be conveyed to Sponsor: Yes ( ), No (X).

Reviewer: Luqi Pei, Ph.D. (HFD-570)

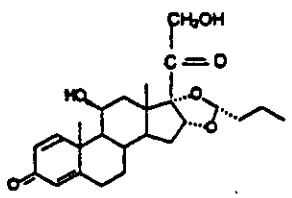
Date of Review Completed: April 15, 1997

Sponsor: Astra USA, Westborough, MA.

Drug Name: *Brand Name:* Rhinocort AQ Nasal Spray
Generic Name: Budesonide

Chemical Name: 16α,17α-butylidenedioxy pregna-1,4-diene-11ß,21 -diol-3,20-dione

Structure:



Formula and Molecular Weight: 430.5

Class: Corticosteroid

Indication: Seasonal or perennial allergic rhinitis in adults and children of 6 year and older

Route of Administration: Nasal Spray

Proposed Clinical Dose: 256 µg/day. (i.e., 4 actuations once a day). This is equivalent to 5.1 µg/kg/day in adults (body weight of 50 kg) and 12.8 µg/kg/day in 6 year old (body weight of 20 kg).

Related INDs and NDAs:

NDA 20441	Pulmicort
NDA 20-233	Rhinocort (budesonide) Nasal Inhaler

Review:

This review only addresses items 7 - 11, 14 and 15 of the submitted Environmental Assessment.

The sponsor claims category exclusions of Item 7 - 11 and did not submit assessment of these items. This is based on the low expected introduction concentration (EIC) of the drug. The EIC is [redacted] ppb that is far less than the qualify threshold of 1 ppb (The expected annual production is less than [redacted] kg). Therefore, the Tier 0 approach is applicable and Items 7 - 11 are not necessary (The CDER guidance For The Submission Of An Environmental Assessment in Human Drug Applications and Supplements - November, 1995).

Item 14 (references) is not applicable.
Item 15 (appendixes) is acceptable.

Recommendation:

Waiving of Items 7 - 11 for this application is acceptable.

/S/ 6/2/97

Luqi Pei, Ph.D.
Pharmacologist/Toxicologist

/S/ 6/2/97

Review completed on April 4, 1997

cc: HFD-570/Division File
HFD-570/ Pei/ Anthracite/ Sheevers/ Himmel

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original Review, NDA fileability

NDA No. 20,746

Serial Nos., Date of Submission:
000 Original Application July 29, 1996

Information to be conveyed to Sponsor: Yes (X), No ( ).

Reviewer: Luqi Pei, Ph.D. (HFD-570)

Date of Review Completed: November 4, 1996

Sponsor: Astra USA, Westborough, MA

Drug Name:
Generic Name: Budesonide
Brand Name: Rhinocort Aqua Nasal Spray

Formulation:	mg/~~µg~~/actuation (mg/50 µl)	**Standard**
	64 (mg) 32 (µg)	
Budesonide		
Cellulose/		NF
Dextrose		USP
Polysorbate 80		NF
Edetate disodium		USP
Potassium sorbate		NF
Hydrochloride acid		NF
Water		USP

Related NDAs: 20233, 20441
Class: Glucocorticosteroid
Indication: Allergic rhinitis (6 year and/or older)
Route of Administration: Intranasal spray

APPEARS THIS WAY
ON ORIGINAL

BACKGROUND:

A pre-NDA meeting of Rhinocort Aqua Nasal Inhaler was held between the Astra USA and the FDA on February 27, 1995. During the meeting, the sponsor expressed their intention to file an NDA. The Agency expressed our concern about the presence of an inactive ingredient, potassium sorbate because the compound was not approved for nasal or inhalation administration. Therefore, the Agency requested that the sponsor supply additional information so that safety of the formulation can be fully evaluated. In response to the Agency's request, the sponsor submitted two documents on March, 1, 1995. One document was the final report of the Cosmetic Ingredient Review Expert Panel on sorbic acid and potassium sorbate (*J Amer Coll Toxicol, 1988;7:837-880*). The panel concluded that sorbic acid and potassium sorbate were safe to use as inactive cosmetic ingredients (1.0%). The other document was a Federal Register publication (*vol. 48, No. 199, Oct. 13, 1983*) which claims potassium sorbate is safe as an active ingredient at concentrations of 1% - 3% in the treatment of vaginal irritation. On March, 17, 1995, the representatives from HFD-570 agreed by teleconferences that the amount of potassium sorbate [redacted] was acceptable based on the Federal Register on the vaginal drug products.

REVIEW:

A brief summary of safety evaluation of the proposed Rhinocort Aqua nasal spray formulation is given in the following table. To simplify the discussion, only the 64 mcg strength formulation is listed. The composition of the 32 mcg strength formulation is essentially identical, except from the lower concentration of active ingredient.

Ingredients	Amount/ actuation (mg/50 µg)	Concen -tration (%)	Approved usage			NDA No.	Drug name
			Route	Concent. (%)	volume (max. µl)		
Budesonide	[redacted]	[redacted]	Nasal	[redacted]	[redacted]	20233	Rhinocort
Cellulose			Nasal			20121	Flonase
Dextrose			Nasal			20121	Flonase
Polysorbate 80			Nasal			20121	Flonase
Edetate disodium			Nasal			20393	Atrovent
Potassium sorbate*			Oral Topical Viginal			74076 [redacted] FR	OTC

* The compound has not been approved for intranasal use.

As highlighted in the table, safety of the two inactive ingredients, potassium sorbate and polysorbate 80, is of concern. Potassium sorbate has never been approved for intranasal or inhalational use in any drug products previously. The lack of data precludes proper evaluation of

the compound by intranasal and/or inhalation administration. The concentration of polysorbate 80 is five times the approved level. Because the proposed volume in rhinocort equals the maximal volume of flonase, the total daily exposure of polysorbate 80 [redacted] mg/person) in rhinocort will be five times the approved dose [redacted] mg/person).

As a food additive potassium sorbate is a GRAS compound (generally regarded as safe, TOMES Databank). The compound is also frequently used as an inactive ingredient (preservative) in oral and topical formulations of therapeutic drug products (a total of 27 NDAs). In these NDAs, potassium sorbate concentration ranged from 0.1% in oral preparations to 0.15% in topical preparations (*Inactive Ingredient Guide of the FDA, 1996*). As the active ingredient, potassium sorbate is safe at concentrations of 1% - 3% in vaginal drug products (*Federal Register, vol. 48, No. 199, Oct. 13, 1983*). The division's previous decision was based on the active ingredient in vaginal dug products. This decision should be re-evaluated.

To facilitate the discussion, the toxicology of potassium sorbate is briefly summarized. According to the Cosmetic Ingredient Review Expert Panel Report (1988), potassium sorbate is practically nontoxic in acute oral studies, slightly irritating at concentrations up to 10%, not tumorigenic at concentrations of 0.1% in the diet and 0.3% in the drinking water, and nor teratogenic in pregnant rats and mice, nor a significant primary sensitizer at concentrations less than 0.5%. Mutagenicity results of the compound were equivocal. Results from genotoxicity studies were inconclusive. Both positive and negative results were obtained in the following testing systems: Ames test, genetic recombination tests, reversion assays, *rec* assays, chromosomal aberration, sister chromosomal exchange, and gene mutation. Wuggler *et al.* (*Mut Res 1992;238:107-111*) reviewed the genotoxic potential of potassium sorbate. They concluded that the compound was weakly genotoxic depending upon the storage condition and the route of administration.

Further exploration argues against extrapolation of vaginal cream data to nasal spray. Firstly, anatomic and physiologic properties of nasal and vaginal mucosa may differ considerably. While it is true that both the nasal cavity and the vagina possess a mucosa layer, the histological structure of the mucosa differs significantly. The vaginal mucosa has a thick layer of the cornified cells, which are rather resistant to chemical and mechanical insults. On the other hand, inner nasal mucosa is thinner, devoid of the cornified layer, fragile and more susceptible. The vagina also possesses a thicker mucous layer which is protective to the epithelial cells. Furthermore, pH and enzymes in the nasal cavity and vagina may differ. Deposition and clearance are also likely to vary considerably for the vaginal and nasal passages. All these indicate a greater uncertainty to extrapolating toxicity between the two routes of administration.

Secondly, the treatment duration of the vaginal irritation may not be applicable to the allergic rhinitis. The treatment for vagina irritation is mostly short term usage. Indication for allergic rhinitis is regarded as chronic use under the current division policy.

Thirdly, interaction between polysorbate 80 and potassium sorbate is unknown. Polysorbate is a surfactant/detergent. It is also used frequently as an absorption enhancer. The

absorption enhancing effect is attributed at least partially to its ability to damage the membrane or other cellular structures. Two carcinogenicity studies of polysorbate 80 (PO and SC) revealed equivocal tumorigenic in rats (*TOMES databank*). In addition, the concentration of polysorbate 80 is [ ] times higher than that previously in intranasal products. As mentioned previously, potassium sorbate is weekly mutagenic. When a week mutagen (potassium sorbate) and a possibly weak carcinogen (polysorbate 80) are used in combination, a synergistic effect in toxicity could occur. Therefore, their carcinogenic potential should be of concern.

The mutagenicity of potassium sorbate and its unknown effect on nasal passage, the high level of polysorbate 80, and the co-administration of the two compounds all contribute to the uncertainty of the safety assessment of these two compounds. To alleviate the above concerns, additional information is necessary. According to the current Division policies, reformulation of a drug product (inactive and active ingredients) needs bridging studies by the intended route of administration with exposure duration(s) of up to 6 months. This is to ensure that the compound of interest is safe by intranasal and/or inhalation administration.

CONCLUSION:

The evaluation of rhinocort budesonide has been completed. Safety of budesonide has been established by other NDAs (20233, 20441), however, safety of two inactive ingredients, namely potassium sorbate and polysorbate 80, has not been established. If no other data is available from the sponsor, additional toxicity study(ies) is necessary to address these issues.

The NDA application is fileable, although additional information is required. This decision is based on the available data and the division's previous decision.

RECOMMENDATION:

The sponsor was informed by teleconference on October 2, 1996 that additional toxicological data are needed to support safe nasal use of potassium sorbate and polysorbate 80 in humans. The sponsor was given the following options:

1. Provide evidence of nasal or relevant routes of administration to support safety evaluation of these two compounds. Or

2. Conduct a 6-month toxicity study(ies) by the intended route of administration in appropriate species to address the safety concern about potassium sorbate and polysorbate 80.

3. If a study is needed, sufficient safety margins should be given during dose selection. The study may be done with the following options:

1. Using the intended clinical formulation. Or
2. Conduct the study with potassium sorbate and polysorbate 80 individually or in combination at the sponsor's discretion.

/S/ 11/4/96

Luqi Pei, Ph.D.
Pharmacologist/Toxicologist

Ori: IND
HFD-570/Division File
HFD-570/Dr. Pei
HFD-570/Dr. Sevak
HFD-570/Dr. Sheevers
HFD-570/Dr. Ng

/S/ 11/4/96

Review completed on 10-2-96.
Revised on 10-15-96.

APPEARS THIS WAY
ON ORIGINAL