CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-441/S002

PHARMACOLOGY REVIEW(S)

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

NDA No. 20-441

Date(s) of Submission: 10/6/97

Information to be Conveyed to Sponsor: Yes (X), No ( )

Reviewer: Lawrence F. Sancilio, Ph.D.

Date Review Completed: 3/9/98

Sponsor: Astra USA,
P.O. Box 4500
Westborough, MA 01581-4500

Drug Name: Primary: Budesonide (Pulmicort)

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

Class: Corticosteroid

Indication: Treatment of bronchial asthma in children ≥ 6 years old and in adults.

Route: Inhalation

Formulation: Pulmicort Turbuhaler is an inhalation-driven multi-dose budesonide micronized dry powder inhaler. Each metered dose is 200 ug of budesonide. The dose delivered from the mouthpiece is 160 ug per actuation. The maximum recommended human daily inhalation doses based on delivery from the mouthpiece are 1280 mcg (8 actuations, 25.6 mcg/kg, 947 mcg/m^2) for adults and 640 mcg (4 actuations, 32 mcg/kg, 800 mcg/m^2) in children, ≥ 6 years old.

Review

The recommended changes are in **bold** or via ~~strikethrough~~.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies were conducted in mice and rats using oral administration to evaluate the carcinogenic potential of budesonide. There was no evidence of a carcinogenic effect when budesonide was administered orally for 91 weeks to mice at doses up to 200 mcg/kg/day (approximately 1/2 the maximum recommended

daily inhalation dose **in adults and children** on a mcg/m^2 basis). In a 104-week **oral** study in Sprague-Dawley rats, a statistically significant increase in the incidence of gliomas was observed in male rats receiving **an** oral dose of 50 mcg/kg/day (approximately the maximum recommended daily inhalation dose on a mcg/m^2 basis); no such changes were seen in male rats receiving oral doses 25 mcg/kg/day (approximately the maximum recommended daily inhalation dose a mcg/m^2 basis) or in female rats at oral doses up to 50 mcg/kg/day (approximately the maximum recommended daily inhalation dose on a mcg/m^2 basis).

Two additional 104-week carcinogenicity studies have been performed with oral budesonide at doses of 50 mcg/kg/day (approximately 1/3 the maximum recommended daily inhalation dose **in adults and children** on a mcg/m^2 basis) in male Sprague-Dawley and Fischer rats. These studies did not demonstrate an increased glioma incidence in budesonide-treated animals as compared with concurrent controls or reference corticosteroid-treated groups (prednisolone and triamcinolone acetonide). Compared with concurrent controls, a statistically significant increase in the incidence of hepatocellular tumors was observed in all three steroid groups (budesonide, prednisolone, triamcinolone acetonide) in these studies.

The mutagenic potential of budesonide was evaluated 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. Budesonide was not mutagenic or clastogenic in any of these tests.

The effect of subcutaneous budesonide on fertility and general reproductive performance was studied in rats. At 20 mcg/kg/day (approximately 1/8 the maximum recommended daily inhalation dose **in adults** on a mcg/m^2 basis), decreases in maternal body weight gain, prenatal viability, and viability of the young at birth and during lactation were observed. No such effects were noted at 5 mcg/kg (approximately 1/32 the maximum recommended daily inhalation dose **in adults** on a mcg/m^2 basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C: As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day **in rabbits** (approximately 1/3 the maximum recommended daily inhalation dose **in adults** on a mcg/m^2 basis) and 500 mcg/kg/day **in rats** (approximately 3 times the maximum recommended daily inhalation dose **in adults** on a mcg/m^2 basis)

No teratogenic or embryocidal effects were observed in rats when budesonide was administered by inhalation at doses **up to** 250 mcg/kg/day (approximately 2 times the maximum recommended daily inhalation dose **in adults** on a mcg/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 corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids

than humans.

Overdosage: The minimal inhalation lethal dose in mice was 100 mg/kg (approximately **320** times the maximum recommended daily inhalation dose **in adults and approximately 380 times the maximum recommended daily inhalation dose in children** on a mcg/m^2 basis). There were no deaths following the administration of an inhalation dose of 68 mg/kg in rats (approximately **430** times the maximum recommended daily inhalation dose **in adults and approximately 510 times the maximum recommended daily inhalation dose in children** on a mcg/m^2 basis). The minimal oral lethal dose was 200 mg/kg in mice **(approximately 630 times the maximum recommended daily inhalation dose in adults and approximately 750 times the maximum recommended daily inhalation dose in children on a mcg/m^2 basis)** and less than 100 mg/kg in rats (**approximately 630** times the maximum recommended daily inhalation dose **in adults and approximately 750 times the maximum recommended daily inhalation dose in children** on a mcg/m^2 basis).

/S/ 2/9/98

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

/S/ March 9, 1998

cc. /Division File, NDA 20-441
/C.S.O., HFD-570
/LFSancilio, HFD-570
/ JSun, HFD-570
ITOCH, HFD-570

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APPEARS THIS WAY
ON ORIGINAL

Drug: **Pulmicort NDA 20-441**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric	6	0.16	4	0.64	20	0.03	25	0.80
Adult	>12	0.16	8	1.28	50	0.03	37	0.95

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	p.o.	0.2	3	0.6	0.63	0.75	½	1/1
rat	p.o.	0.05	6	0.3	0.32	0.38	1/3	1/3
hamster			4	0	—	—	—	—
rat	p.o.	0.025	6	0.15	0.16	0.19	1/6	1/5
rat			6	0	—	—	—	—
Reproduction and Fertility:								
mouse			3	0	—	N/A	—	N/A
rat	sc	0.02	6	0.12	0.13	N/A	1/8	N/A
rat	sc	0.005	6	0.03	0.03	N/A	1/32	N/A
rat	inhal	0.25	6	1.5	1.58	N/A	2	N/A
Teratogenicity:								
mouse			3	0	—	N/A	—	N/A
rat	sc	0.5	6	3	3.17	N/A	3.0	N/A
rabbit	sc	0.025	12	0.3	0.32	N/A	1/3	N/A
rabbit			12	0	—	N/A	—	N/A
extra			—	—	—	N/A	—	N/A
Overdosage:								
mouse	inhal	100	3	300	316.72	375.00	320	380
mouse	p.o.	200	3	600	633.45	750.00	630	750
rat	inhal	68	6	408	430.74	510.00	430	510
rat	p.o.	100	6	600	633.45	750.00	630	750
Other:	(Describe studies here)							
dog			20	0	—	—	—	—
dog			20	0	—	—	—	—
dog			20	0	—	—	—	—
extra			—	—	—	—	—	—
extra			—	—	—	—	—	—