CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-929

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

TROUT

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Labeling Reivew

NDA 20-929	Reviewer: Young Moon Choi, Ph.D. Submission: 2/9/00
Drug: Budesonide Nebulizing Suspension (Pulmicort Respules ™)	Reviewed: 6/28/00
	PDUFA due date: 8/9/00
Sponsor: Astra USA	

Synopsis

Pulmicort Respules contain budesonide formulated as a suspension for inhalation via a nebulizing system. The proposed maximum dose is [redacted] mg/day for the maintenance treatment and prophylactic therapy of asthma in a pediatric population aged [redacted] to 8 years. The Human Pharmacokinetics component of the NDA was reviewed previously by Brad Gillespie (Refer to the Clinical Pharmacology and Biopharmaceutics reviews of 3/20/98, 5/14/98, 5/15/98, and 12/31/98).

The purpose of this review is to evaluate the Pharmacokinetic section of the proposed package insert labeling. Rather than provide individual comments, relevant sections of the labeling are reproduced below, with modifications highlighted in underline/strikeout as follows:

Pharmacokinetics

The activity of PULMICORT RESPULES is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was two times as active as the 22S epimer. *In-vitro* studies indicated that the two forms of budesonide do not interconvert.

Budesonide is primarily cleared by the liver. In asthmatic children 4-6 years of age, the terminal half-life of budesonide after inhalation is 2.3 hours, and the systemic clearance is 0.5 L/min, which is approximately 50% greater than in healthy adults after adjustment for differences in weight.

After a single dose of 1 mg budesonide, a peak plasma concentration of 2.6 nmol/L was obtained approximately 20 minutes after nebulization in children 4-6 years of age. The exposure ([redacted] AUC) of budesonide following administration of a single 1 mg dose of budesonide by nebulization to asthmatic children 4-6 years of age is comparable to healthy adults given [redacted] a single 2 mg dose by nebulization.

Absorption: In asthmatic children 4-6 years of age, the total absolute bioavailability (*i.e.*, lung + oral) following administration of PULMICORT RESPULES via jet nebulizer was approximately 6% of the labeled dose.

The peak plasma concentration of budesonide occurred 10-30 minutes after start of nebulization.

Distribution: In asthmatic children 4-6 years of age, the volume of distribution at steady-state of budesonide was 3 L/kg, approximately the same as in healthy adults. Budesonide is 85-90% bound to plasma proteins, the degree of binding being constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended doses. Budesonide showed little or no binding to corticosteroid-binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism: *In-vitro* studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 3A catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in-vitro* and *in-vivo* metabolic patterns has been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion: Budesonide is excreted in urine and feces in the form of metabolites. In adults, approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

Special Populations: No differences in pharmacokinetics due to race, gender or age have been identified.

Hepatic Insufficiency: Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous pharmacokinetics of budesonide were, however, similar in cirrhotic patients and in healthy adults.

Recommendation

The Office of Clinical Pharmacology and Biopharmacetuics, Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) reviewed the package insert. It is found to be acceptable provided that it is modified as described above.

/S/ 6/28/00

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

Ramana Uppoor, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 20-929; Div file; HFD-570 (Trout),
HFD-870(Uppoor, Huang, Hunt, Choi), CDR (B. Murphy)

APPEARS THIS WAY
ON ORIGINAL

Trout

DEC 31 1998

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-929	**Type of Submission:**
Budesonide nebulizing suspension	Response to AE Letter
(PULMICORT RESPULES™)	**Submission Dates:**
Astra USA	8/7/98
PO Box 4500	**Reviewer:**
Westborough, MA 01581-4500	Brad Gillespie, PharmD

Background Pulmicort Respules contain budesonide formulated as a suspension for inhalation via a nebulization system. The proposed maximum dose is — mg/day for the maintenance treatment and prophylactic therapy of asthma in a pediatric population aged — to 8 years. The Human Pharmacokinetics component of this NDA was reviewed previously by Brad Gillespie (see Clinical Pharmacology & Biopharmaceutics Reviews of 3/20/98, 5/14/98 and 5/15/98). The purpose of this review is to evaluate the Pharmacokinetics section of the proposed package labeling. Rather than provide individual comments, relevant sections of the labeling are reproduced below, with modifications highlighted in redline/strikeout.

PHARMACOKINETICS The activity of PULMICORT RESPULES is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.
Budesonide is primarily cleared by the liver. In young asthmatic children 4-6 years old, the terminal half-life of budesonide after inhalation is 2.3 hours, and the systemic clearance is 0.5 L/min, which — healthy adults after adjustment for differences in weight.
After a single dose of 1 mg budesonide, a peak plasma concentration of 2.— nmol/L was obtained approximately 20 minutes after nebulization in young children 4-6 years of age. — The exposure (AUC) of budesonide following administration of a single 1 mg dose of budesonide — by nebulization to —
Absorption —

[1] Data obtained after oral administration to adults is not relevant to this product.

The peak plasma concentration of budesonide occurred about 10-30 min after start of nebulization.

Distribution

, the volume of distribution at steady-state of budesonide was 3 L/kg, approximately the same as in healthy adults. Budesonide is 85-90% bound to plasma proteins, the degree of binding being constant over the concentration range (1-100 nmol/L) achieved with and exceeding recommended doses. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism

In vitro studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 3A catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns have been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion

Budesonide — excreted in urine and feces in the form of metabolites. In adults, approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

Special Populations

Hepatic Insufficiency

Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous pharmacokinetics of budesonide were , however, similar in cirrhotic patients and in healthy adults.

Recommendation The revised proposed package labeling for this product has been reviewed by the Office of Clinical Pharmacology & Biopharmaceutics and it has been found to be acceptable provided that it is modified as described above.

/S/ 12/28/98

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

/S/ 12/31/98

FT _____ Ramana Uppoor, PhD, Team Leader

cc:
HFD-570 (NDA 20-929, Divisional File, Trout, Chu)
HFD-870 (ChenME, Hunt, Uppoor)
CDR (Barbara Murphy)

MAY 15 1998

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-929	**Type of Submission:**
Budesonide nebulizing solution	Response to Comments
(PULMICORT RESPULES)	**Submission Dates:**
	4/23/98
Astra USA	
PO Box 4500	**Reviewer:**
Westborough, MA 01581-4500	Brad Gillespie, PharmD

The last outstanding comment from the original Clinical Pharmacology & Biopharmaceutics review of this application is summarized below:

The sponsor needs to verify that the pivotal study batch (Studies 03-3043: TE 357 and 04-3104: XF 531) formulations were the same as that of the to-be-marketed product.

In a 5/15/98 telephone conversation between the sponsor and this reviewer, it was resolved that *Composition D*, the formulation used for both of these studies, is the same as the to-be-marketed formulation, as described on page 5 of Volume 1.3 of the original NDA.

Thus, this final Clinical Pharmacology & Biopharmaceutics Comment is now satisfactorily resolved.

LSJ 5/15/98

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

LSJ 05/15/98

FT Ramana Uppoor, PhD., Team Leader

cc:
HFD-570 (NDA 20-929, Divisional File, Trout, Chan)
HFD-870 (ChenME, Hunt, Uppoor)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)

MAY 1 4 1998

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-929	**Type of Submission:**
Budesonide nebulizing solution	Response to Comments
(PULMICORT RESPULES')	**Submission Dates:**
	4/23/98
Astra USA	**Reviewer:**
PO Box 4500	Brad Gillespie, PharmD
Westborough, MA 01581-4500	

In the original Clinical Pharmacology & Biopharmaceutics review of this application (see 3/20/98 Review), the following Comment was generated:

- The sponsor is requested to provide further information describing the formulation used for this study (all entries marked *not existing* from the INVESTIGATIONAL FORMULATIONS-PHARMACOKINETICAL STUDIES table, page 59, volume 1.17).

It was communicated to the sponsor in a April 7, 1998 fax. In this response, the sponsor confirms that the batch records from that batch were destroyed one year after their expiration dates and no information is currently available. In a followup telephone conversation with the sponsor, Astra assured the agency that although the batch records were not available, the batch's formulation was the same as that of the to-be-marketed product. FDA responded that they should submit something quantitative to substantiate that claim.

If this new data does indicate that the batches are comparable, then the sponsor's response to this Comment is acceptable. In its absence, it remains unresolved.

/S/ 5/14/98

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

/S/ 05/14/98

FT Ramana Uppoor, PhD., Team Leader

cc:
HFD-570 (NDA 20-929, Divisional File, Trout, Chan)
HFD-870 (ChenME, Hunt, Uppoor)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)

MAR 20 1998

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-929	**Type of Submission:**
Budesonide nebulizing solution	NDA, 3P
(PULMICORT RESPULES™)	**Submission Dates:**
	11/18/97
Astra USA	02/06/98
PO Box 4500	**Reviewer:**
Westborough, MA 01581-4500	Brad Gillespie, PharmD

Synopsis Pulmicort Respules is budesonide formulated as a suspension for inhalation (via a nebulizer). The proposed maximum dose is [redacted] µg/day for the maintenance treatment and prophylactic therapy of asthma in a pediatric population aged [redacted] to 8 years. The sponsor currently markets Pulmicort Turbuhaler (dry powder inhaler) and Rhinocort (intranasal budesonide) for use in adults. Although this product has a stand alone safety and efficacy program, it would be useful to compare the systemic bioavailability of this product relative to the approved inhalation product. In support of this application, the sponsor has submitted the results of clinical safety and efficacy studies as well as several pharmacokinetic trials. In this review, two human pharmacokinetic studies were evaluated. The first study was chosen because it characterized the pharmacokinetics and bioavailability of the product in a pediatric population. The second, because it provided a bioavailability linkage between the proposed and the approved inhalation product in an adult population.

Pediatric The absolute budesonide bioavailability ($F_{systemic\ (nominal)}$ = nominal dose normalized $AUC_{nebulized}/AUC_{intravenous}$) after nebulization with the Pari LC Jet nebulizer was 6.1%. After administration of 1 mg budesonide nebulizing suspension (BNS) a peak plasma concentration of 2.59 (CV· [redacted], nmol/L was observed 0.33 (range: [redacted], hours after dosing. Total exposure ($AUC_{0-\infty}$) was 10.9 (CV· [redacted]) nmol·hr/L

Adult The absolute budesonide bioavailability ($F_{systemic\ (nominal)}$ = nominal dose normalized $AUC_{nebulized}/AUC_{intravenous}$) after nebulization with the Pari LC Jet Plus system was 15.5%. Pulmicort Turbuhaler's absolute bioavailability is approximately 38%. Since the maximum daily dose of the two products are similar (Turbuhaler: 1600 µg/day; BNS: 2000 µg/day) total budesonide exposure should be less from the BNS product than from the Turbuhaler. Total exposure ($AUC_{0-\infty}$) data obtained after dosing 1 mg budesonide via the Turbuhaler compared to that after 2 mg BNS supports this hypothesis ($AUC_{Turbuhaler}$: 10.30 nmol·hr/L, CV· [redacted] vs AUC_{BNS}: 9.90 nmol·hr/L, CV· [redacted]). After administration of 2 mg budesonide nebulizing suspension with the Pari LC Jet Plus nebulizer, a peak plasma concentration of 4.02 (CV· [redacted] nmol/L was observed 0.27 (range: [redacted] hours after dosing. Data from this study should be interpreted with caution because the assay was not optimally validated and the formulation used was not well characterized.

Background The sponsor received FDA approval for budesonide dry powder inhaler (PULMICORT Turbuhaler™) on June 24, 1997. This product is a budesonide nebulized suspension (BNS) proposed for the maintenance treatment of asthma and prophylactic therapy in children aged [redacted] to 8 years. Since there are no other inhaled corticosteroids approved for this age group, this application has received a priority ("P") review.

This product is available in [redacted] strengths: [redacted], 0.25 mg/mL and 0.5 mg/mL. In all cases, 2 mL of the suspension will be administered, providing a total budesonide dose of 0.25, 0.5 [redacted] mg.

Since this product is a stand alone product with regard to both safety and efficacy, a strict bioavailability linkage between it and the approved dry powder inhaler (DPI) is not needed. Nevertheless, it is useful to compare budesonide exposure after administration via different devices. Although in the Phase I trials of this product a variety of different nebulizer systems were tested, the pivotal safety and efficacy study used only the Pari LC Jet Plus nebulizer. Therefore, only data obtained with this system will be reported in the summary section. For complete data from all systems, see the individual study reports.

Formulations The definitive pediatric pharmacokinetic study (04-3104) was conducted using the product intended for marketing. According to the sponsor, documentation is not available to describe the formulation used in the adult study (03-3043).

Bioavailability

Adult The absolute budesonide bioavailability ($F_{systemic\ (nominal)}$ = nominal dose normalized $AUC_{nebulized}/AUC_{intravenous}$) after nebulization with the Pari LC Jet Plus system was 15.5%. When based on the delivered dose (nominal dose - budesonide recovered on the dosing apparatus) the observed absolute bioavailability ($F_{systemic\ (delivered)}$) was 64.4%. Data from this study should be interpreted with caution because the assay was not optimally validated and the formulation used was not well characterized.

Pediatric The absolute budesonide bioavailability ($F_{systemic\ (nominal)}$ = nominal dose normalized $AUC_{nebulized}/AUC_{intravenous}$) after nebulization with the Pari LC Jet nebulizer was 6.1%. When based on the delivered dose (nominal dose - budesonide recovered on the dosing apparatus) the observed absolute bioavailability ($F_{systemic\ (delivered)}$) was 26.3%.

Summary In an adult population, the absolute bioavailability of BNS is approximately 16% compared to Pulmicort Turbuhaler's absolute bioavailability of 38%. Since the maximum daily dose of the two products are similar (Turbuhaler: 1600 µg/day; BNS: [redacted] µg/day) total budesonide exposure should be less from the BNS product than from the Turbuhaler in an adult population. Total exposure ($AUC_{0-\infty}$) data obtained after dosing 1 mg budesonide via the Turbuhaler compared to that after 2 mg BNS supports this hypothesis ($AUC_{Turbuhaler}$: 10.30 nmol·hr/L vs AUC_{BNS}: 9.90 nmol·hr/L).

Pharmacokinetics
The sponsor did not submit a satisfactory multiple-dose study (in an adult or pediatric population). Based on the 2 hour elimination half-life observed in the intravenous dosing arm of adult study 03-3043, an accumulation factor ($R_{ac}=(1/1-e^{-k\tau})$ of approximately 1.015 would be expected if this product is dosed every 12 hours. If dosed once daily, a R_{ac} of 1.00 is anticipated. Thus, substantial accumulation after repeat dosing is not likely, obviating the need for a multiple-dose pharmacokinetic trial.

Adult After administration of 2 mg budesonide nebulizing suspension with the Pari LC Jet Plus nebulizer, a peak plasma concentration of 4.02 (CV-) nmol/L was observed 0.27 (range:) hours after dosing. Total exposure ($AUC_{0-\infty}$) was 9.90 (CV-) nmol·hr/L. Data from this study should be interpreted with caution because the assay was not optimally validated and the formulation used was not well characterized.

Pediatric Parameters reported are non-parametric estimates derived from the analysis of a semi-simultaneous study. After administration of 1 mg budesonide nebulizing suspension with the Pari LC Jet Plus nebulizer, a peak plasma concentration of 2.59 (CV-) nmol/L was observed 0.33 (range:) hours after dosing. Total exposure ($AUC_{0-\infty}$) was 10.9 (CV-) nmol·hr/L.

Assay In the pivotal adult pharmacokinetic trial (03-3043), the sponsor used a LC-MS method with a sensitivity of In the pediatric study (04-3104), a more sensitive method was employed (lower limit of quantitation:). The sponsor has not provided any cross-assay validation data. With regard to assay performance data, quality control samples were inadequate to fully assess the reliability of the assay used for Study 03-3043 since the low level control ( ) was below the lower limit of quantification of the assay ( ). Assay performance from the pivotal pediatric trial (04-3104) was satisfactory.

Comments (Pertains to the pivotal adult study, 03-3043)
1. Quality control (QC) samples were not ideal for fully assessing the reliability of the assay since the low level control ( ) was below the lower limit of quantification of the assay ( ). Assay performance is best validated by choosing at least 2 (ideally, 3) QC samples evenly distributed along the range of the standard curve.
2. The sponsor is requested to provide further information describing the formulation used for this study (all entries marked *not existing* from the INVESTIGATIONAL FORMULATIONS-PHARMACOKINETICAL STUDIES table, page 59, volume 1.17).

Recommendation The sponsor has adequately characterized the pharmacokinetics of inhaled budesonide suspension in a pediatric population. Nevertheless, the bioavailability linkage of this product to the approved dry powder inhaler is founded on study 03-3043, which has at least two flaws: inadequate documentation of assay performance and an poorly characterized formulation. The weakness of this linkage should be considered when evaluating the safety database of this product.

Please forward Comments 1 - 2 to the sponsor. The sponsor is requested to respond to Comment 2 and Comment 1 is for their general reference

ISI 3/20/98

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

3/24/98

ET ISI Mei-Ling Chen, PhD., Division Director, Division of Pharmaceutical Evaluation II

cc:
HFD-570 (NDA 20-929, Divisional File, Trout, Chu, Meyer)
HFD-870 (ChenME, Hunt)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)

Systemic availability and pulmonary deposition of budesonide inhaled as nebulized suspension from three different nebulizers

Study No. 03-3043 **Volume** 1.20 **Pages** 1 - 392
Investigator Sam Lindgren: Clinical Phase I Unit, Astra Draco
Study Dates 3/94 - 6/94
Analytical Facility Astra Draco
Analysis Dates 8/12/94 - 9/16/94

OBJECTIVES To determine the systemic availability and pulmonary deposition of budesonide after inhalation of nebulized suspension using different brands of nebulizers.

TREATMENTS

- Budesonide, 2mg inhaled via Pari Inhalierboy nebulizer
- Budesonide, 2mg inhaled via Pari LC Jet Plus nebulizer
- Budesonide, 2mg inhaled via Maxim MA-2 nebulizer
- Budesonide, 4mg via oral administration
- Budesonide, 0.5mg via intravenous infusion

STUDY DESIGN A total of 12 healthy adult volunteers (10 male, 2 female) were included in this open-label, randomized, single-dose, 5-treatment, 5-period crossover study. After an overnight fast, subjects received a single dose of study medication. Volunteers continued fasting and remained ambulatory for 4 hours after study drug administration. At this time, regular meals were served. A washout interval of at least 7 days separated the dosing periods. Subjects were confined throughout each study phase. Blood samples were obtained for plasma budesonide determinations just prior to (zero hour), 10, 30 and 60 minutes, 2, 4, 6 and 8 hours after study drug administration.

ASSAY A LC-MS method was used for plasma budesonide determinations. Validation data included in this submission were inadequate to fully assess assay performance. Details of these inadequacies are described in Comment 2, below.

ASSAY PERFORMANCE

Linearity	Satisfactory: Standard Curve linear from [redacted]
Accuracy	Unsatisfactory: [redacted]
Precision	Unsatisfactory: CV- [redacted]
Sensitivity	LOQ: [redacted]
Specificity	Satisfactory: Chromatograms submitted

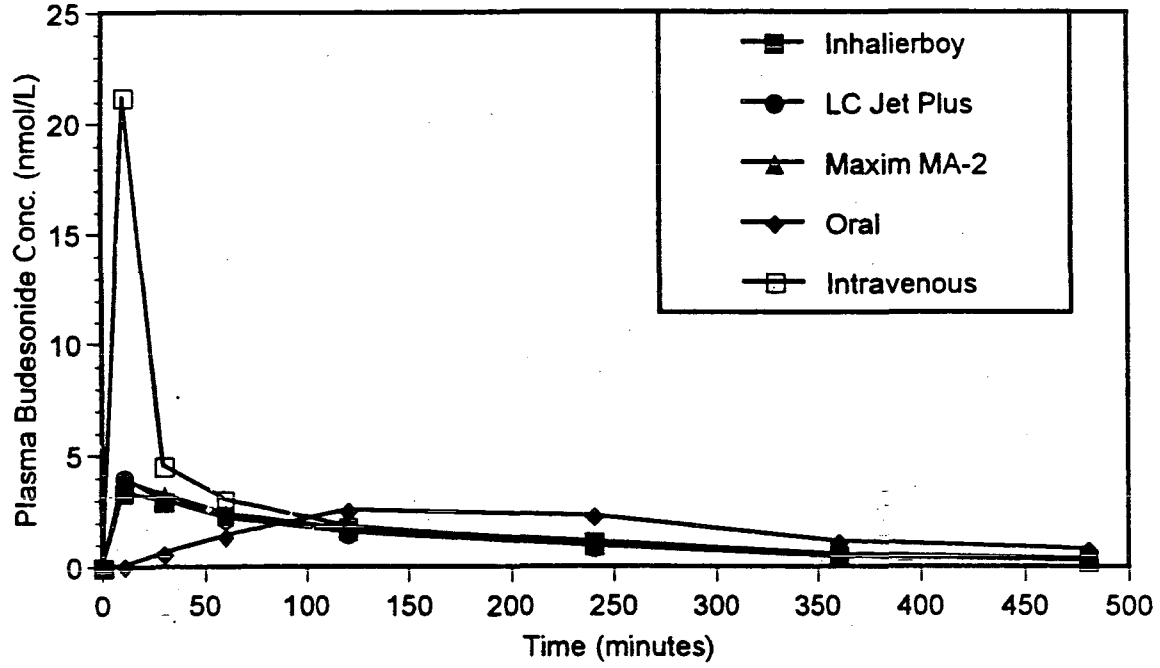
DATA ANALYSIS

Pharmacokinetic: $AUC_{0-\infty}$, CL, MRT, $t_{1/2}$, Vd, Vss after intravenous dosing; $AUC_{0-\infty}$, C_{max}, T_{max}, F_{syst} amd F_{lung}[1] after oral and inhalation dosing

Statistical: Descriptive statistics were provided for all treatment groups. Additionally, for oral treatments and inhalations, an ANOVA model with factors Subject, Period and Treatment was used to estimate mean and confidence limits for pharmacokinetic parameters and differences (quotients).

RESULTS All of the original 12 subjects completed all phases of the study. The mean plasma concentration versus time profiles for the first 8 hours after dosing are presented in Figure 1 (all formulations) and Figure 2 (inhalation and oral capsule formulations). Intravenous and extravascular pharmacokinetic parameters are presented and compared in Tables 1 and 2, respectively.

Figure 1. Mean Plasma Budesonide Concentration versus Time Profile after Administration of Budesonide via Inhalierboy, LC Jet Plus and Maxim MA-2 Nebulizers (2mg), Oral Capsule (4mg) and Intravenous Injection (0.5mg)



[1] $F_{lung} = (F_{syst}-F_{oral})/(100-F_{oral})$ where F_{oral} was the systemic bioavailability after oral administration

Figure 2. Mean Plasma Budesonide Concentration versus Time Profile after Administration of Budesonide via Inhalierboy, LC Jet Plus and Maxim MA-2 Nebulizers (2mg) and Oral Capsule (4mg)

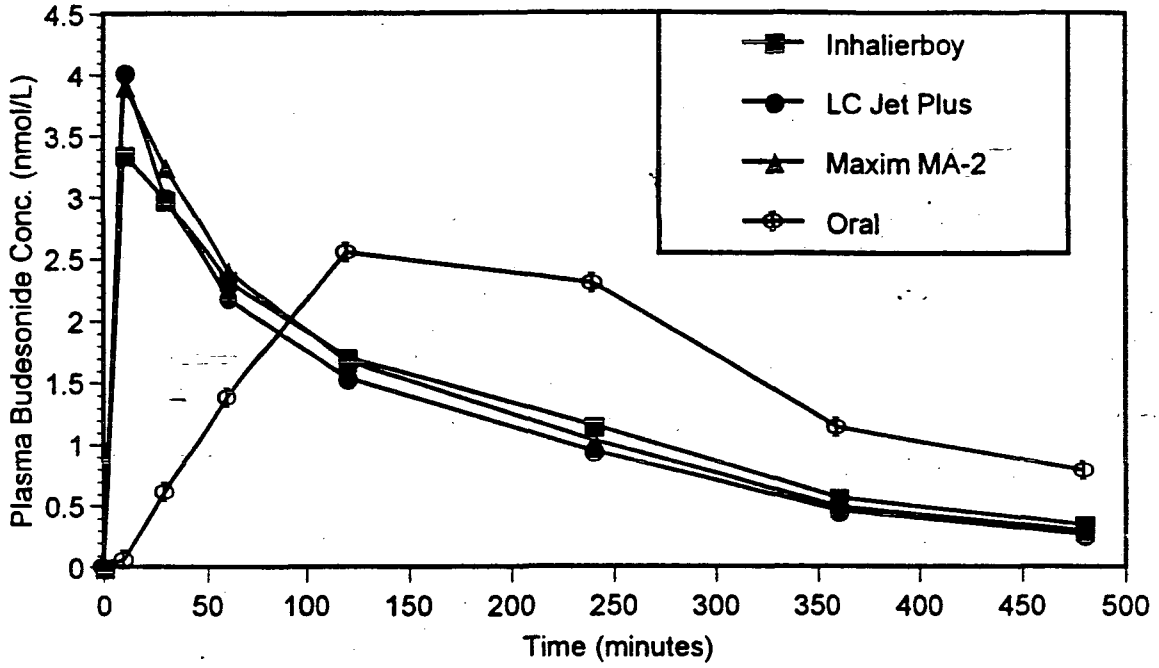


Table 1. Mean Budesonide Pharmacokinetic Parameters After Intravenous Administration

	Dose	*$t_{1/2}$*	*AUC*	*MRT*	*CL*	*Vd*
mean	1173	1.96	16.1	1.97	1279	216
unit	nmol	hour	nmol•hr/L	hour	mL/min	L
% CV						

Table 2. Mean (%CV) Budesonide Pharmacokinetic Parameters After Extravascular Administration

	Unit	*Oral Capsule*	*Inhalierboy*	*LC Jet Plus*	*Maxim MA-2*
Dose	**nmol**	**9281**	**1833 (18)**	**1109 (22)**	**1237 (21)**
$AUC_{0-\infty}$	**nmol•hr/L**	**15.1 (54)**	**11.1 (35)**	**9.90 (41)**	**10.7 (28)**
MAT	**hour**	**2.80 (17)**	**1.39 (20)**	**1.09 (27)**	**1.12 (32)**
C_{max}	**nmol/L**	**2.82 (59)**	**3.96 (43)**	**4.02 (38)**	**4.37 (20)**
T_{max}[2]	**hour**	**3 (1-4)**	**0.27 (.23-.53)**	**0.27 (.17-.33)**	**0.44 (.28-1.03)**
$F_{syst\ (nominal)}$[3]	**%**	**11.9 (50)**	**17.6 (27)**	**15.5 (31)**	**17.1 (23)**
$F_{syst\ (delivered)}$[4]	**%**	**---**	**45.7 (29)**	**64.4 (30)**	**65.4 (22)**

[2] *median (range)*

[3] Dose normalized $AUC_{extravascular}/AUC_{intravenous}$

COMMENTS

1. The batch used for this study (TE 357) is not well described in the submission. In the investigational formulations table, the notation "n.e." (*not existing*) appears in most all of the columns describing the production of this batch. The sponsor is requested to provide information to more fully describe this batch.
2. Quality control (QC) samples were not ideal to fully assess the reliability of the assay since the low level control ( ) was below the lower limit of quantification of the assay ( ). Assay performance is best validated by choosing at least 2 (ideally, 3) QC samples evenly distributed along the range of the standard curve.

CONCLUSION

The absolute bioavailability of this nebulized budesonide product is approximately 15 - 17%. Data from this study should be interpreted with caution because the assay was not optimally validated and the formulation used was not well characterized (described in Comments 1 - 2, above).

[4] Dose (nominal dose - budesonide recovered on dosing apparatus) normalized $AUC_{extravascular}/AUC_{intravenous}$

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-929
Compound:	Budesonide Nebulizing Suspension
Submission Date:	11/18/97
Sponsor:	Astra USA, Inc.
Type of Submission:	Original New Drug Application
Code:	3P
Consultant Reviewer:	Raymond Miller, D.Sc.

BIOAVAILABILITY OF NEBULIZED BUDESONIDE IN YOUNG CHILDREN

Report No.: 04-CR-3104

Study Title: Systematic Availability and Pharmacokinetics of Budesonide (Pulmicort®) Suspension for Nubulization when Administered by a JetNebulizer (Pari LC Jet Plus™) in Young Asthmatic Children.

Investigator and Study Site: [redacted]

Objective: The primary objective of the study was to determine the absolute systemic availability of budesonide nebulizing suspension in young children using a jet nebulizer (Pari LC Jet Plus connected to the Pari Master compressor). The secondary objective was to determine basic pharmacokinetic parameters of intravenous and nebulized (via Pari LC Jet Plus) budesonide in young children.

Subjects: Thirteen asthmatic children, 3.5 to 6 years old, were included in the study. Ten patients completed both the intravenous and the inhaled treatments, all of which were Caucasian, eight being boys and two being girls. The average age of the patients completing both administrations was 4.7 years. One patient was 3.5 years old, three were 4 years old, four were 5 years old, and two were 6 years old. The average height was 109 cm (range: 95.5-121.0) and the average weight was 18.4 kg (range: 15.0-25.5).

Study Design: Open-label, semi-simultaneous with one intravenous and one inhaled treatment, fixed order with the inhaled dose given 3 h after the intravenous dose, single center.

Formulation, Dosage and Administration: Budesonide solution for injection 25 µg/mL, 5 mL diluted to 20 ml (total dose of 0.125 mg) batch No DXD 18, intravenous infusion during 10 minutes. Budesonide nebulizing suspension 0.5 mg/mL, 2 mL (total dose 1.0 mg), batch No XF 531, inhalation via Pari LC Jet Plus connected to Pari Master compressor, nebulization time fixed to 5 min. The actual dose delivered to the patient was calculated by subtracting the sum of the amounts of budesonide recovered after nebulization from the ampoule, the expiratory filter, the nebulizer with mouthpiece and connecting tubes, and the mouth rinsing water.

Blood Sampling and Analysis: Venous blood samples for budesonide analysis were collected before the start of infusion (0), at the end of infusion (10 min), at 15, 30. 60, 90, 120 min after the start of infusion (immediately before inhalation); at the end of inhalation (at 5 min after start of inhalation or as soon as possible), at 20, 40, 80, 160, 240, 330, 360 min after the start of inhalation.
Plasma concentration of the sum of the two budesonide epimers was determined by a [redacted] method. Within day precision was [redacted], at LOQ) and between day precision was [redacted] at LOQ). Accuracy was [redacted]. The lower limit of quantification was [redacted]

Data Analysis and Results:

Nonparametric estimates of pharmacokinetic parameters were calculated as follows: The terminal elimination rate constant was estimated from the last three blood levels (plus) using linear regression. The i.v. and the inhalation curves were separated from each other by assuming that the terminal phase for the intravenous dose was reached when the inhalation started, three hours after the i.v. dose. Pharmacokinetic parameters including bioavailability were calculated with 95% confidence limits. The results are presented in table 1.

A pharmacokinetic model was fit to the plasma concentration data using a nonlinear mixed effect model approach. A three exponential model best described the data. Absorption after inhalation was modeled as a zero-order process to describe the transport of drug from the nebulizer to the lungs. The drug was then assumed to be absorbed into plasma by a first-order process. The results are presented in table 1.

This reviewer analyzed the data independently using a different nonlinear mixed effect modeling algorithm (NONMEM). The model used was the same as the parametric model described above, i.e. three compartment model with zero-order delivery by the nebulizer and first order absorption from the lung. The results are presented in table 1.

Estimated Pharmacokinetic Parameters			
Parameter (units)	Nonparametric Analysis Mean (95% CI)	3-exponential model Mean (95% CI)	FDA analysis Mean (95% CI)
Cl (mL/min)	536 (461-623)	504 (436-576)	527 (432-622)
Vss (L)	55 (45-68)	64 (51-78)	51 (41-61)
F_{DTS}	26.3 (20.3-34.1)	24.2 (19.1-30.6)	26.7 (14.8-41.5)
$AUC_{0-\infty}$ (i.v.) ng·hr/mL	8.27 (3.7-12.8)	-	-
$AUC_{0-\infty}$ (nebulize)[1] ng·hr/mL	4.7 (2.4-7.0)	-	-
C_{max} (nebulize)[1] ng/mL	1.12 (0.4-1.9)	-	-
T_{max} (min)	17.4 (6.6-28.2)	-	-

[1]Dose to patient depends on individual nebulization

Sponsor's Conclusion: Systemic availability of the Dose to Subject (F_{DTS}) in asthmatic children 3.5 to 6 years old is 26.3% (20.3-34.1) using a nonparametric model. Only part of the nebulized dose reaches

the patient and calculating the amount of labeled dose that reaches the patient the systemic availability of the labeled dose was estimated as 6.1% (4.6-8.1). A parametric evaluation with a three-exponential model gave similar results. Clearance in this population was estimated as 536 mL/min (461-623) and steady-state volume of distribution as 55 L (45-68).

Reviewers Comment: The semi-simultaneous design used to determine the bioavailability of budesonide is acceptable under the circumstances, i.e. compliance in young children and inter-occasion variability. This model dependent approach has been shown to give reliable results. The so called parametric approach relies on fitting the terminal slope after nebulization and assuming that this applies to the intravenous dose. With the relatively short half life of budesonide this should not present a problem in extrapolating the data. The semi-simultaneous approach, however, is essentially a model dependent method. Analysis by the reviewer shows that the fit of the three-exponential model to the data is very good (fig 1, 2 and 3) and provides estimates that are similar to the sponsors nonparametric and parametric estimates (table 1) of the pharmacokinetic parameters.

3 Page(s) Withheld

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Clinical Pharmacology & Biopharmaceutics Review

NDA 20-929
Budesonide nebulizing solution
(PULMICORT RESPULES™)

Astra USA
PO Box 4500
Westborough, MA 01581-4500

Type of Submission:
NDA, 3P
Suitability for filing
Submission Date:
11/18/97

Reviewer:
Brad Gillespie, PharmD

Background

The sponsor received FDA approval for budesonide dry powder inhaler (PULMICORT Turbuhaler™) on June 24, 1997. This product is a budesonide nebulized suspension (BNS) proposed for the maintenance treatment of asthma and prophylactic therapy in children aged —— to 8 years. Since there are no other inhaled corticosteroids approved for this age group, this application will most likely receive a priority ("P") review. The purpose of this review is to establish the suitability of the human pharmacokinetic section of this application for filing.

This product is available in — strengths: ——— , 0.25 mg/mL and 0.5 mg/mL. In all cases, 2 mL of the suspension will be administered, providing a total budesonide dose of 0.25, 0.5 —— mg.

Since this product is a stand alone product with regard to both safety and efficacy, a strict bioavailability linkage between it and the approved dry powder inhaler (DPI) is not needed. Nevertheless, it is important to be able to compare budesonide exposure after administration via different devices. The absolute bioavailability of this product is slightly lower than that of the approved product in adults (16% of the labeled dose versus 38% of the labeled DPI dose), but the dose administered is higher (maximum dose 1.0 mg versus 0.4 mg) and the pediatric volume of distribution is most likely smaller than that of adults. Thus, while comparable plasma budesonide concentrations are anticipated in an adult population, it is expected that this product would provide higher levels in children than those observed after the DPI product is administered to adults. This potential difference in exposure should be evaluated in an across-study comparison and kept in mind when the safety database for this product is evaluated

Studies Submitted

In addition to four pivotal clinical safety and efficacy trials, the sponsor conducted a total of 2 Pediatric and 3 adult BNS pharmacokinetic (PK) trials. A variety of pediatric and adult studies using other budesonide formulations were also submitted.

Pediatric PK BNS Studies

(Study 04-3104) *Systemic availability and pharmacokinetics of budesonide suspension for nebulization when administered by a jet nebulizer (Pari LC Jet Plus) in young asthmatic children*

A single-dose absolute bioavailability study using a semi-simultaneous design. It enrolled 10 asthmatic children, 3.5 to 6 years of age. This is the pivotal pediatric pharmacokinetic study.

(Study H10-0025) *Pharmacokinetics of budesonide in children after intravenous administration and oral inhalation*

A single-dose absolute bioavailability study which included oral inhalation via a pressurized metered dose inhaler (pMDI) with spacer and the Pari Inhalierboy nebulizer. In an attempt to limit the number of blood samples required, smaller samples were collected during the first hour after dosing and pooled into a single sample for each patient, thus representing area under the curve for the first hour ($AUC_{0\text{-}1h}$).

Adult BNS PK Studies

(Study 04-3043) *Systemic availability and pulmonary deposition of budesonide inhaled as nebulized suspension from three different nebulizers*

A five-way single-dose crossover study. The five treatments were: intravenous, oral capsules and nebulized suspension administered via [redacted], the Pari LC Jet Plus and the [redacted] nebulizers.

(Study SD-004-0017) *Pulmonary deposition and systemic availability of budesonide inhaled from an [redacted] nebulizer, Pari LC Jet Plus, in healthy subjects. A follow-up to Study 04-3043.*

Seven of the healthy subjects that participated in Study 04-3043 were enrolled in this trial. The subjects were given one single inhaled dose of budesonide from the Pari LC Jet Plus with a [redacted]

(Study 004-2151) *An attempt to find clinically equivalent doses of budesonide administered from a pressurized metered dose inhaler or as a suspension for nebulization. Estimation of lung deposition from plasma concentration of budesonide.*

Adult asthmatics were treated with inhaled budesonide in a randomized three-way, multiple-dose crossover study. The three treatments were: pMDI with spacer and [redacted] 1 mg bid and 4 mg bid.

Studies 04-0134 and 04-3043 should be adequate to characterize the pharmacokinetics and absolute bioavailability of BNS in a pediatric and adult population, respectively.

Comments

1. Sample pooling in Study H10-0025 is unacceptable since it is not capable of capturing peak plasma drug concentrations. Thus, this study is not adequate to support any labeling claims
2. With regard to the proposed package insert, the sections are annotated to identify studies which support labeling claims.
3. The submission provides formulation information which details the composition of the product. The definitive pharmacokinetic studies were conducted using the product intended for marketing.
4. Assay methodology and validation were sufficiently described in the submission.
5. On its face, the Human Pharmacokinetics section of NDA 20-929 is organized, paginated and is adequately legible to allow an efficient and thorough review.

Recommendation

The Office of Clinical Pharmacology & Biopharmaceutics briefly reviewed the Human Pharmacokinetics section of NDA 20-929 and found it adequate to permit filing.

/S/ 12/16/97

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

FT /S/ 12/16/97 Dale P. Conner, PharmD,

cc:
HFD-570 (NDA 20-929, Divisional File, Trout, Chu)
HFD-870 (ChenME, Hunt)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)