AstraZeneca

DRUG PRODUCT	Pulmicort Turbuhaler	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Budesonide	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SD-004-CR-0601		
VERSION NO.	01		
STUDY CODE	SD-004-0601		
DATE	07 November, 2001		

FINAL

A comparison of the relative systemic availability of budesonide in asthmatic patients after inhalation from the current US version of Pulmicort® Turbuhaler® and from two strengths of the new version of Pulmicort® Turbuhaler®

STUDY CENTRE(S)

Single centre study

PUBLICATION (REFERENCE)

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST patient ENROLLED**	January 30, 2001	Clinical pharmacology
- **DATE OF LAST patient COMPLETED**	April 02, 2001	

OBJECTIVES

The primary aim was to compare the relative rate and extent of the systemic availability of budesonide inhaled via Pulmicort Turbuhaler M0 (4 x 200 μg) and via Pulmicort Turbuhaler M3 (4 x 180 μg) and to test for bioequivalence. The area under the curve ($AUC_{0-\infty}$) and the maximum concentration (C_{max}) were the primary variables.

As a secondary aim, the dose strength equivalence of the two strengths of Pulmicort Turbuhaler M3 (8 x 90 μg and 4 x 180 μg) were compared using $AUC_{0-\infty}$ and C_{max}.

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STUDY DESIGN

The study was of an open, randomized, cross-over design. Each patient inhaled budesonide as a single dose via Turbuhaler on three separate treatment days.

DIAGNOSES AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Well-controlled adult asthmatic (as defined by the American Thoracic Society) patients.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

a. Pulmicort (budesonide) Turbuhaler version M3, powder inhaler, 90 μg/inhalation, metered dose (80 μg/inhalation delivered dose), 60 doses, batch No. BL 11. Given as a single dose of 720 μg (8x90 μg metered dose).

b. Pulmicort (budesonide) Turbuhaler version M3, powder inhaler, 180 μg/inhalation, metered dose (160 μg/inhalation delivered dose), 60 doses, batch No. BL 12. Given as a single dose of 720 μg (4x180 μg metered dose).

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Pulmicort (budesonide) Turbuhaler version M0, powder inhaler, 200 μg/inhalation, metered dose (160 μg/inhalation delivered dose), 200 doses, batch No. BC 199. Given as a single dose of 800 μg (4x200 μg metered dose).

Training device

Empty placebo Turbuhaler inhalers for both versions; M3 (batch No. BF 11) and M0 (batch No. ZI 19).

DURATION OF TREATMENT

Each patient inhaled budesonide as a single dose on three separate treatment days. The study days were separated by a wash-out period of at least 5 days.

MAIN MEASUREMENT(S) AND VARIABLE(S):

- **PHARMACOKINETIC**

Pharmacokinetic parameters, with $AUC_{0-\infty}$ and C_{max} as the primary variables, and C_{12h} and T_{max} as the secondary variables, were calculated and compared between the M0 and the M3 versions of Turbuhaler.

- **SAFETY**

Adverse events were collected by means of standard questions. Laboratory measurements, vital signs and ECG recordings were performed at entry (visit 1) and at follow-up (visit 5).

METHODS FOR DATA EVALUATION

From plasma concentrations of budesonide, the $AUC_{0-\infty}$, C_{max}, C_{12h} and T_{max} were determined with standard non-parametric methods. The pharmacokinetic parameters of the M0 and the M3 versions of Pulmicort Turbuhaler were compared with an analysis of variance (ANOVA) model with fixed factors for patient, visit and treatment. For $AUC_{0-\infty}$, C_{max}, and C_{12h} a multiplicative model was used, and for T_{max} an additive model. Bioequivalence will be declared if the 90% confidence intervals for the ratios of $AUC_{0-\infty}$ and C_{max} for the M3 and M0 versions fall within 0.8-1.25. This was tested between the two versions, M0 200 μg/inhalation and M3 180 μg/inhalation, and between the two strengths of the M3 version of Pulmicort Turbuhaler.

Secondary variables were compared using a 5% significance level.

PATIENTS

Thirty-eight (38) patients were enrolled into the study and 37 patients (15 female and 22 male) were randomized.

	Total
No. planned	36
No. randomized and treated	37/37
Men/Women	22/15
Mean age (range)	31,0 (19-61)
No. analysed for pharmacokinetics	36
No. analysed for safety	37
No. completed	36

SUMMARY

- PHARMACOKINETIC RESULTS

Bioequivalence was shown for the comparison between Pulmicort Turbuhaler M3 4 $\times$180 μg and Pulmicort Turbuhaler M0 4 $\times$200 μg on both $AUC_{0-\infty}$ and C_{max}, i.e. the 90% confidence interval for the ratio fell between 80 and 125%. Also the comparison between the two strengths of the Pulmicort Turbuhaler M3 inhaler passed the equivalence test on both parameters. The results are summarized below in Tables 1 and 2

Table 1. Bioequivalence test of plasma budesonide $AUC_{0-\infty}$

Treatment ratios	**ratio (%)**	**90 % C. I.**	
M3 4×180 μg / M0 4×200 μg	96.3	90.9	102.1
M3 4×180 μg / M3 8×90 μg	92.2	87.0	97.7

Table 2. Bioequivalence test of plasma budesonide C_{max}

Treatment ratios	**ratio (%)**	**90% C. I.**	
M3 4×180 μg / M0 4×200 μg	100.4	92.1	109.4
M3 4×180 μg / M3 8×90 μg	94.4	86.6	102.9

- SAFETY RESULTS

The treatments were well tolerated by the patients in this study. No clinically safety related findings were identified.

DATE OF THE REPORT

September 25, 2001