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| DRUG PRODUCT Symbicort Turbuhaler® DRUG SUBSTANCE(S) Symbicort Turbuhaler® DOCUMENT NO. SD-039-CR-0617 VERSION NO. 01 STUDY CODE SD-039-0617 DATE 5 June, 2000 | <h2>Synopsis</h2> <p>REFERRING TO PART OF THE DOSSIER</p> | (FOR NATIONAL AUTHORITY USE ONLY) |
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FINAL

Onset of Action of Symbicort Turbuhaler® compared with Seretide DiskusTM in asthmatic patients

STUDY CENTRE

Single-center study

PUBLICATION (REFERENCE)

STUDY PERIOD

- DATE OF FIRST PATIENT ENROLLED 99-10-05
- DATE OF LAST PATIENT COMPLETED 00-04-05

PHASE OF DEVELOPMENT

IIIB

OBJECTIVES

The primary objective was to compare the onset of action of Symbicort Turbuhaler 160/4.5 µg and 2x (160/4.5) µg with that of Seretide Diskus 50/250 µg when single doses were given to asthmatic patients with reversible lung function.

Safety was a secondary objective.

The main variable was FEV₁.

STUDY DESIGN

Single-center study with a four-way crossover, double-blind, double-dummy design. Symbicort Turbuhaler 160/4.5 μg and 2x (160/4.5) μg , Seretide Diskus 50/250 μg and placebo were given as single doses. FEV₁ was monitored for 3 hours.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Inclusion criteria: Out-patients (men or women), age 18-75 with asthma in stable condition. Baseline FEV₁ \geq 60% of predicted normal and at least 1.5 L. Reversibility in FEV₁ \geq 15% of baseline. Written informed consent.

Exclusion criteria: Allergy to investigational drugs or lactose. Significant disease or disorder. Change in prescribed asthma medication or significant respiratory infection within 30 days of visit 1. Women who were pregnant, breast-feeding or planning a pregnancy, or not using acceptable contraceptives, or were not surgically sterile. Participation in a clinical study within 30 days of visit 1.

Criteria for discontinuation: Incorrect inclusion, pregnancy.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Symbicort Turbuhaler (budesonide/formoterol) 160/4.5 μg and 2x (160/4.5) μg , single doses by inhalation.

Batch No: ZM 16

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Seretide Diskus (salmeterol/fluticasone) 50/250 μg , single dose by inhalation.

Batch No: DAH 1

DURATION OF TREATMENT

Single doses

MAIN VARIABLES:

- EFFICACY

The primary efficacy variable was average FEV₁ during the first 15 minutes following inhalation of study drug (E₀₋₁₅).

Secondary variables were:

average FEV₁ during the 3 hour observation interval after inhalation (E_{av, (0-3h)})

maximum FEV₁ (E_{max}),

time to half maximum FEV₁ (T_{max50%}),

FEV₁ recorded 3 minutes after inhalation (E_{3min}),

FEV₁ recorded 3 hours after inhalation (E_{3h}), and

time to 15% increase in FEV₁ from baseline (T_{onset}).

- SAFETY

Safety was assessed by adverse events.

STATISTICAL METHODS

The parameters $E_{0-15\text{min}}$, $E_{3\text{min}}$, E_{max} , $E_{\text{av,(0-3h)}}$ and $E_{3\text{h}}$ were analysed using multiplicative models, i.e. the logarithm of the response was used and treatment differences were expressed as ratios of geometric means. An analysis of variance model with patient, period and treatment as fixed factors and the pre-drug FEV_1 as covariate (log-transformed) was fitted to data and the treatments were then compared pairwise.

$E_{0-15\text{min}}$ and $E_{\text{av,(0-3h)}}$ were calculated as the AUC (calculated using the trapezoidal method) divided by the observation time.

The onset of effect, T_{onset} and $T_{\text{max50\%}}$, was compared pairwise between the active treatments using Wilcoxon's signed rank test. Patients not having a 15% increase within the first hour were assigned a value of 60 minutes in the comparison of T_{onset} .

The sensitivity of the results for $E_{0-15\text{min}}$ and $E_{3\text{min}}$ was investigated by computing the following variant of Cook's distance.

PATIENTS

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| No. planned | 30 |
| No. randomised and treated | 30 |
| Males/Females | 15/15 |
| Mean age (years) | 49.4 (28-73) |
| Baseline values | |
| Mean FEV ₁ (L) | 2.54 (1.48-4.28) |
| Mean FEV ₁ (% pred) | 78.2 (61-99) |
| Mean reversibility (% baseline), 0.1 mg | 12.1 (4.9-22.1) |
| Mean reversibility (% baseline), 0.1 mg + 0.4 mg | 19.1 (12.3-31.5) |
| No. analysed for efficacy | 30 |
| No. analysed for safety | 30 |
| No. completed | 30 |

All randomised patients received all four treatments: placebo, Symbicort 160/4.5 μ g, Symbicort 2x (160/4.5) μ g and Seretide 50/250 μ g.

SUMMARY**- EFFICACY RESULTS**

Onset: The primary variable, average FEV₁ during the first 15 minutes following inhalation of study drug ($E_{0-15\text{min}}$) was statistically significantly increased for Symbicort Turbuhaler both at 160/4.5 μ g and 2x 160/4.5 μ g compared to Seretide Diskus 50/250 μ g. There was no evidence of a difference between the two Symbicort Turbuhaler doses. For FEV₁ at 3 min following inhalation of study drug, both doses of Symbicort Turbuhaler showed a statistically significant increase compared to Seretide Diskus. There was no statistically significant difference between Seretide Diskus and placebo. Time to half maximum FEV₁ ($T_{\text{max } 50\%}$) was statistically shorter for both Symbicort Turbuhaler doses compared to Seretide Diskus. There was no evidence of a difference between Symbicort Turbuhaler doses. Defined as 15% increase in FEV₁ within 60 min after dose, both doses of Symbicort Turbuhaler gave a statistically significantly faster onset than Seretide Diskus. There was no evidence of a difference between Symbicort Turbuhaler doses. The relative rate of onset for 160/4.5 μ g and 2x (160/4.5) μ g Symbicort Turbuhaler was estimated to be 8.6 and 12.2 times faster than for Seretide Diskus respectively. Time to onset of effect (T_{onset}) was compared for all patients. Fourteen patients (47%) showed an onset after inhalation of 50/250 μ g Seretide Diskus, 22 (73%) after inhalation of 160/4.5 μ g Symbicort Turbuhaler, and 23 (77%) after inhalation of 2x (160/4.5) μ g Symbicort Turbuhaler.

Overall effect: Overall effect was evaluated with regard to the average FEV₁ during the 3 hour observation interval ($E_{\text{av}(0-3\text{h})}$), the maximal FEV₁ (E_{max}) and FEV₁ at 3 hours ($E_{3\text{h}}$). 2x (160/4.5) μ g Symbicort Turbuhaler gave statistically significantly larger increases than Seretide Diskus for all three parameters. 160/4.5 μ g also gave statistically significant larger

increases for $E_{av(0-3h)}$ and E_{max} compared to Seretide Diskus. For E_{max} the difference between the two Symbicort Turbuhaler doses was on the borderline of being statistically significant, but otherwise there was no evidence of a difference between 160/4.5 and 2x (160/4.5) μg Symbicort Turbuhaler.

- **SAFETY RESULTS**

The reported adverse events (AEs) were mainly respiratory disorders, β_2 -agonist class effects or isolated symptoms, not considered to signal any new safety information or any differences between treatments. Most of the adverse events were of mild intensity. No AE of severe intensity was reported. There were no serious AEs, no other significant AEs or discontinuations due to AEs in the study.