AstraZeneca

SD-037-0287

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Oxis®

ACTIVE INGREDIENT: formoterol

Trial title (number): A double-blind, randomized, placebo controlled cross-over study to compare the bronchodilatory effect of formoterol inhaled via two different Turbuhaler devices.

Development phase:IIIa
First subject recruited: 17 April 1999
Last subject completed: 20 September 1999
Approval date: 08 March 2000

OBJECTIVES

To compare the bronchodilatory effect of formoterol, 4.5μg/dose, inhaled via two different Turbuhaler devices (marketed version and new version) in adult patients with persistent asthma.

METHODS

STUDY DESIGN

The study was of a five-way, cross-over, randomized, double-blind and placebo-controlled design. The patients visited the clinic six times, including enrolment on Visit 1. On Visit 2, throughout Visit 6, the patient inhaled a single dose of placebo, 4.5 μg or 18 μg of formoterol through the marketed or new version of Turbuhaler.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Adult patients with stable asthma.

1. Male or female out-patients > 18 years.
2. Signed informed consent prior to any study related procedures.
3. Comply with the instructions on the use of Turbuhaler.
4. FEV_1prebronchodilator at Visit 1 should be >40 % of predicted normal value and >1.5 L.
5. FEV_1reversibility >15%, 30 minutes after inhaling 0.5 mg terbutaline from Bricanyl Turbuhaler.

TEST PRODUCT, DOSAGE AND MODE OF ADMINISTRATION

Oxis Turbuhaler, new version, 4.5 μg/dose (delivered dose, corresponding to 6 μg metered dose), 60 doses.

COMPARATOR PRODUCT, DOSAGE AND MODE OF ADMINISTRATION

Oxis Turbuhaler, marketed version, 4.5 μg/dose (delivered dose, corresponding to 6 μg metered dose), 60 doses.

Placebo Oxis Turbuhaler, marketed version, 60 doses.

Placebo Oxis Turbuhaler, new version, 60 doses.

DURATION OF TREATMENT
Single doses

MAIN VARIABLE(S):
- EFFICACY
Primary variable: 12-hour average FEV_1(Eav) measured after a single dose of the study medication.

- SAFETY
Pulse, blood pressure and adverse events.

STATISTICAL METHODS
The 12-hour average FEV_1 was compared between treatments using a multiplicative analysis of variance model with patient, visit and treatment as fixed factors and the pre-drug FEV_1 as a co-variate. The relative dose potency for the new version compared to the marketed version was estimated by fitting parallel lines to the estimated means. Pulse and blood pressure were evaluated by comparing the change from pre-drug value to 20 minutes after inhalation of the drug, between the treatments. The adverse events were analysed by the Drug Safety at AstraZeneca R&D Lund by means of descriptive statistics and qualitative analysis.

RESULTS

PATIENTS

	Total
No. planned	50
No. randomized and treated*	60
Males/Females	32/28
Mean age (range)	46.5 (20-70)
FEV_1 (% predicted) (range)	71.1 % (4.1-91.7)
Reversibility (range)	21.2 % (14.6-59.6)
No. analysed for efficacy	60
No. analysed for safety	60
No. completed**	57
* 62 patients were enrolled and randomized	
** 57 patients completed all visits	

EFFICACY RESULTS
Mean FEV_1 during 12 hours (Eav), were 2.29 L (placebo), 2.45 L (4.5 µg; new version), 2.42 L (4.5 µg; marketed version), 2.52 L (18 µg; new version) and 2.49 L (18 µg; marketed version). No statistically significant differences were found between the inhalers on the 4.5 µg dose level, on the 18 µg dose level or between the 4.5 µg and the 18 µg dose levels. However, a statistically significant dose-response was found when the data from the marketed and the new versions of

Turbuhaler were pooled, although the slope was very low 0.020 (95% C.I.: 0.005-0.035). This allowed only a very rough estimate of the relative dose-potency between the inhalers, 1.8 (95% C.I.: 0.6-27).

Analysis of maximum FEV_1 (E_{max}) showed that all active doses were statistically significantly better than placebo. A significant difference was also found between the 4.5 µg and 18µg doses of the marketed version of Turbuhaler (0.1 L). The 95% C.I. for the relative dose-potency between the inhalers, based onE_{max}, ranged between 0.7 and 5.2.

Onset of effect was estimated from FEV_1 measured at 3 minutes after inhalation of the study doseE_{3min}. All active doses were significantly more effective than placebo at 3 minutes. In addition, a small but significant difference was found between the 4.5µg and 18µg doses of the marketed version of Turbuhaler (0.08 L).

SAFETY RESULTS
The only AE with a treatment related distribution was tremor, after inhalation of 18µg formoterol. Two discontinuations due to AE were reported, but no serious AE. There were no clinically important changes in vital signs over time. Individual values generally showed small changes which were not considered clinically important.

REFERENCES
None at this time

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Oxis™ (formoterol), Healthcare Professionals should view their specific country information.