Nome della società: Astra Draco AB
Lund, Sweden
Nome del prodotto: Bambuterol®
Nome dell'ingrediente attivo: Bambuterol tablets/oral solution
Terbutaline tablets/oral solution
Codice studio: 09-3033
Numero rapporto: 09-CR-3033

CLINICAL STUDY SYNOPSIS

Title of the study: A one-year safety study with bambuterol once daily and terbutaline three times daily in 2-12 year old children with asthma.

Principal Investigator(s): Austria: Jasminka P. Zarkovic, M.D., Johann Wank, M.D., Tomas Frischer, M.D. Belgium: Willy Lipschutz, M.D., Isidor Dab, M.D. Finland: Erkka Valovirta, M.D., Anna-Leena Kuusela, M.D., Marianne Marenk, M.D. Germany: Dietrich Berdel, M.D., Hermann Kalhoff, M.D. Sweden: Göran Oldeus, M.D., Bengt Persson, M.D., Grazyna Sandahl, M.D. UK: David John Scott, M.D., Robin Smith, M.D.

Study centre(s): The study was a multicentre study performed at 15 centres in Austria, Belgium, Finland, Germany, Sweden and UK.

Publication (reference): -

Study period: 940210-961113

Clinical phase: IIIA

Objectives: The aim of this study was to compare bambuterol oral solution/tablets administered once daily in the evening with terbutaline oral solution/tablets administered three times daily, during one year, in 2-5 year old children (oral solution) and in 6-12 year old children (tablets) with asthma. The primary objective was to evaluate safety using pulse rate, blood pressure, adverse events, haematology, clinical chemistry and, plasma terbutaline and bambuterol concentrations. The secondary objective was to evaluate efficacy using FEV1 and the subjective asthma control assessment.

Study design: The study was of an open, randomised, parallel-group design, and lasted for one year.

Number of patients (total and for each treatment): A total of 141 patients were randomized and treated with the study drugs, i.e. 43 patients in the terbutaline group (30 on oral solution and 13 on tablets) and 98 patients in the bambuterol group (62 on oral solution and 36 on tablets).

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Clinical study synopsis

Diagnosis and criteria for inclusion: The patients were to be 2-12 year old boys and girls with asthma. All children with a medical condition indicating regular treatment with an oral bronchodilator on a daily basis might be included in the study, as judged by the investigator.

Investigational drugs, dose and mode of administration, batch No.: Bambuterol hydrochloride (Bambec®) 20 mg tablets. Batch number: SF 251, TC 255, UB 257. Bambuterol hydrochloride (Bambec®) oral solution 1 mg/mL (blackcurrant flavour). Batch number: DTB 57, UM 11, DTF 58.

Reference drugs, dose and mode of administration, batch No.: Terbutaline sulphate (Bricanyl®) 2.5 mg tablets. Batch number: SC 218, UH 230. Terbutaline sulphate (Bricanyl®) oral solution 0.3 mg/mL (raspberry taste). Batch number: TB 680, UL 739.

Duration of treatment: The 6-12 year old children were given bambuterol tablets 10 mg once daily in the evening for 2 weeks and then bambuterol tablets 20 mg once daily in the evening during the remainder of the study if the treatment was well tolerated, or terbutaline tablets 2.5 mg three times daily during the whole study. To check that the patients had not experienced any adverse events which might be due to an increased dose of bambuterol, the investigator contacted the parent/legal guardian per telephone, 2 weeks after visit 2 i.e. after 4 weeks’ treatment. If necessary, the investigator could decrease the dose to 10 mg bambuterol once daily. The 2-5 year old children received bambuterol oral solution 10 mg once daily in the evening or terbutaline oral solution 0.075 mg/kg body weight three times daily. The initial dose, bambuterol oral solution 10 mg once daily in the evening or terbutaline oral solution 0.075 mg/kg body weight three times daily, could be increased or decreased by 50% after two weeks of treatment, depending on lack of efficacy or disturbing adverse events. To check that the patients had not experienced any adverse events which might be due to the initial dose or an increased dose of the study drug, the investigator contacted the parent/legal guardian per telephone, 2 weeks after visit 2 i.e. after 4 weeks’ treatment. If the dose was unchanged or increased at visit 2, the investigator could decrease the dose to bambuterol 5 or 10 mg once daily or terbutaline 0.0375 or 0.075 mg/kg body weight three times daily.

Assessment methods: Adverse events [visit 2-6], blood pressure and pulse rate [visit 1-6], haematology and clinical chemistry [visit 1, 4 and 6], plasma terbutaline/bambuterol [visit 1-4 and 6], Subjective asthma control assessment [visit 2-6] and FEV_{1.0} [visit 1, 3-6. (only 6-12 year old children)].

Statistical methods: The data was analysed by ANOVA.

Summary of results: There were no clinically important differences between the treatment groups concerning pulse rate, systolic or diastolic blood pressure. However, systolic blood pressure at visit 6 showed a statistically significant difference between the treatments, but the absolute difference (-3.2 mmHg) was small and not clinically important.

There were no remarkable findings on the laboratory tests (B-Haemoglobin, B-Leucocytes, S-ALAT, S-ASAT, S-Bilirubin, S-Creatinine, S-Creatine Kinase, S-Potassium, B-Glucose). The only statistically significant difference which was detected between the treatments was for B-Glucose. However, even if the difference was statistically significant, it was numerically small and not clinically important.

Mean steady state plasma terbutaline concentration ranged between 8.0-11.5 nmol/L in the bambuterol tablet group and between 10.6-15.2 in the terbutaline tablet group. The corresponding values in children on oral solution were 10.3-11.3 in the bambuterol group and 7.5-9.7 in the terbutaline group.

FEV_{1} increased with more than 0.2 L in both treatment groups during the year in the study. The subjective opinion on asthma control assessed by the parent/legal guardian showed that good control was achieved. Both treatment groups were similar in this respect.

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Both terbutaline and bambuterol were well tolerated and the reported adverse events were mostly mild to moderate.

Conclusion: Both bambuterol tablets/oral solution once daily and terbutaline tablets/oral solution three times daily showed a good safety profile with respect to clinical and laboratory tests. Both treatments were generally well tolerated and the reported adverse events were mostly mild to moderate. Finally, FEV₁ increased by more than 0.2 L in both treatment groups during the year in the study.