similar to that in adults1. This suggests that drug delivery by inhalation via pMDI plus spacer is lower in children as compared to adults resulting in similar exposure due to the lower body size of the paediatric population. Therefore guideline recommendations of a reduced dosage regimen in children could be appropriate for DPI administration only.
References: 1. Onhøj J, Thorsson L, Bisgaard H. Lung deposition of inhaled drugs increases with age. Am J Respir Crit Care Med. 2000;162 (5):1819-22.

#80 - PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENT OF PRESSURISED METERED-DOSE INHALED BECLOMETASONE/FORMOTEROL IN ADOLESCENT ASTHMA

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Purpose of the study: Asthmatic adolescents are generally recommended to be dosed like adults. However, this population is unique in many ways and limited pharmacokinetic (PK) and pharmacodynamic (PD) data are available on fixed combinations of inhaled-corticosteroids/long acting β2-agonists (ICS/LABA). In addition the influence of age on the systemic exposure of drugs administered via pMDI with or without valved holding chamber is still not fully elucidated. The aim of the study was to investigate the PK/PD profile of a fixed dose combination of ICS/LABA pMDI in asthmatic adolescents with or without valved holding chamber in comparison to a free combination of licenced pMDI products. A comparison of adolescent and adult asthmatics was also conducted.
Methods: Open label, randomized, three-way crossover study, on 30 asthmatic adolescents receiving a single dose of the fixed combination of beclometasone dipropionate (BDP)/formoterol pMDI 100/6 μg per actuation (Foster®) with or without AeroChamber PlusTM or a free combination of BDP 100 μg pMDI (Qvar) plus formoterol 6 μg pMDI (Atimos). An open, parallel arm of 30 asthmatic adults receiving Foster® was added as a control. All patients received a total single dose of BDP and formoterol of 400 μg and 24 μg, respectively. Assessments were performed over 8 hours.
Results: In adolescents, Foster® with or without AeroChamberPlusTM was equivalent to Qvar® + Atimos® or Foster® alone in terms of systemic exposure (AUC0-t) to beclometasone-17-monopropionate (B17MP, active metabolite of BDP) and formoterol; 90% confidence intervals (CIs) for the geometric means ratio fixed/free were all within the 0.80–1.25 range interval. After treatment with Foster® the systemic exposure to B17MP and formoterol was also comparable between adolescents and adults (90% CIs within 0.78–1.17). The PD profile was equivalent between all treatments in terms of plasma potassium, plasma glucose, pulse rate and forced expiratory volume in one-second.
Conclusions: In adolescents the PK and PD of Foster® with or without AeroChamberPlusTM, is comparable to that of a free combination of licensed single entity pMDIs, which have established safety and efficacy profiles. The findings in adolescents adults were comparable.
Reflections stimulated by the research: These results support the indication for use of ICS/LABA pMDIs in adolescents at the same dosage as in adults.

#82 - BRONCHODILATING EFFECTS OF EXTRAFINE BECLOMETASONE DIPROPIONATE AND FORMOTEROL FUMARATE VIA PRESSURIZED METERED DOSE INHALER IN ASTHMATIC CHILDREN

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Introduction: in asthmatic children older than 5 years, the GINA guidelines 2012 update recommend to add inhaled long-acting β2- agonists (LABA) when the disease is not adequately controlled with inhaled corticosteroids (ICS) alone. Controlled studies have shown that fixed combination therapies are as effective as giving each drug separatelyand may increase patients' compliance. A paediatric extrafine fixed combination of beclometasone dipropionate (BDP) and formoterol fumarate (FF) via pressurized metered dose inhaler (pMDI) containing 50 μg of BDP and 6 μg of FF per actuation (CHF1535) was developed by Chiesi Farmaceutici S.p.A. (Parma, Italy).
Methods: in a phase-2, double blind, randomised, active- and placebo-controlled, 5-period cross-over study, the bronchodilator effect of a single administration of CHF1535 (2 actuations, total dose BDP 100 μg and FF 12 μg) was compared to that of a free combination of licensed extrafine BDP pMDI 50 μg (2 actuations, total dose 100 μg) plus FF 6 μg pMDI (2 actuations, total dose 12 μg) in 56 asthmatic children aged $\geq$5 and $<$ 12 years. The primary objective was to demonstrate the non-inferiority of CHF1535 vs the free combination in terms of forced expiratory volume during the first second (FEV1) AUC corrected by time over 12 hours following the morning dose (AUC0–12 h) (primary efficacy variable). Secondary objective was to explore the dose-related efficacy of different doses of CHF1535 (BDP 50 μg/FF 6 μg, BDP 100 μg/FF 12 μg and BDP 200 μg/FF 24 μg) in terms of FEV1 AUC0–12 h. All treatments were administered with AeroChamber Plus spacer device. Safety was assessed through monitoring of adverse events (AEs), ECG and vital signs.
Results: the non-inferiority of CHF1535 100/12 μg compared to the free combination of BDP 100 μg + FF 12 μg in terms of FEV1 AUC0–12 h was demonstrated (adjusted mean difference (95% CI): −0.004 L (−0.050, 0.041) as the lower confidence limit of the 95% CI of the adjusted mean difference was - greater than the non-inferiority limit set at −0.1 L. All treatment groups showed an increase from pre-dose in mean FEV1 at each time-point over the period to 12 hours post-dose. A trend towards a dose-related efficacy response, (FEV1 AUC0–12 h) was shown. The comparisons of each CHF1535 dose vs placebo were: 0.037 L ($P = 0.160$), 0.119 L ($P < 0.001$) and 0.094 ($P < 0.001$) for CHF1535 50/6, CHF1535 100/12, CHF1535 200/24, respectively. No serious AEs were reported during the study and no safety signals were found in terms of ECG and vital signs.
Conclusion: CHF 1535 100/12 μg was non-inferior to the free combination of BDP + FF at the same dose in terms of lung function over the 12-hour post-dose period and a trend towards a dose-related efficacy response was seen. All treatments were safe and well tolerated.
Reflections stimulated by the research: according to the above results, the 100/12 μg dose was selected for the pivotal phase-3 studies of CHF1535 clinical development.