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Indacaterol a novel inhaled once a day β_2 adrenoceptor agonist for the treatment of asthma and chronic obstructive pulmonary disease

Agents that act as agonists of the β_2 adrenoceptor are effective in the management of asthma and chronic obstructive pulmonary disease, primarily through their bronchodilating properties. Current long acting inhaled β_2 adrenoceptor have a bronchodilating effect lasting for 12 hours after a single inhalation and are therefore given twice daily. Indacaterol (5-[(R)-2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one), previously known as QAB149, was discovered in a program to identify compounds with a duration of action compatible with once-daily dosing in man, combined with a fast onset of action and an increased therapeutic index compared to the available inhaled β_2 adrenoceptor agonists (salbutamol, formoterol and salmeterol).

In pre-clinical models, indacaterol is close to a full agonist at the human β_2 adrenoceptor ($E_{max} = 73 \pm 1\%$ of isoprenaline's maximal effect, $pEC_{50} = 8.06 \pm 0.02$) while salmeterol displays only partial efficacy ($38 \pm 1\%$). The functional selectivity profile of indacaterol over β_1 human adrenoceptors is similar to that of formoterol, whereas its β_3 adrenoceptor selectivity profile is similar to that of formoterol and salbutamol. In isolated superfused guinea pig trachea, indacaterol has a fast onset of action (30 ± 4 min) similar to formoterol and salbutamol, and a long duration of action (529 ± 99 min) comparable to salmeterol. In the conscious guinea pig, when given intratracheally as a dry powder, indacaterol inhibits serotonin-induced bronchoconstriction for at least 24 hours while salmeterol, formoterol and salbutamol have durations of action of 12, 4 and 2 hours, respectively. When given via nebulization to anesthetized rhesus monkeys, all compounds dose-dependently inhibit methacholine-induced bronchoconstriction, although indacaterol produces the most prolonged bronchoprotective effect and induces the lowest increase in heart rate for a similar degree of anti-bronchoconstrictor activity. In conclusion, the pre-clinical profile of indacaterol suggests that this compound has a superior duration of action compatible with once-daily dosing in man, together with a fast onset of action and an improved cardiovascular safety profile over marketed inhaled β_2 adrenoceptor agonists.

A randomised, double-blinded, placebo-controlled, crossover, multicentre Phase II clinical study shows that in asthmatic patients, when given once a day, indacaterol has a fast onset of action (clinically relevant bronchodilator activity seen within 5 minutes) and a duration of action up to 24 hours. In addition, no clinically meaningful effect on QTc, blood pressure, pulse rate, potassium, glucose up to four times the expected clinical doses, once daily for up to 28 days are demonstrable.

In summary, the pre-clinical and clinical profile of indacaterol suggests that this compound represents a new generation of inhaled β_2 adrenoceptor agonists. As a single enantiomer, indacaterol combines a long duration of action, compatible with once-daily dosing in man, together with a fast onset of action and an improved cardiovascular safety profile.