



New Inhaled Formulations for the Treatment of Asthma in Children and Adolescents

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Asthma is the most common chronic condition affecting children in the United States. More than 10 million children under age 18 (14%) have been diagnosed with asthma and 6.8 million children (9%) remain with this condition.¹ Inhaled medications (e.g. inhaled corticosteroids and both short and long-acting beta₂-agonists) are the mainstays of asthma treatment. Adherence to medication regimens involving the use of one or more inhaled formulations is often low, with some estimates suggesting that children generally take only 50-60% of prescribed doses.² Adherence is particularly problematic in the pediatric population owing to the coordination required to use some inhaled formations and dosing schedules requiring administration of these inhaled formulations two or three times a day. Additionally, many of these patients must rely on the assistance of caregivers for administration. Several new products have been developed which require less coordination between breath and dose actuation and less frequent dosing.

New Drug Products

Fluticasone furoate

On August 20, 2014, fluticasone furoate inhalation powder (Arnuity™ Ellipta®) was approved by the Food and Drug Administration (FDA) as maintenance treatment of asthma in patients aged 12 years and older. Fluticasone furoate is an inhaled corticosteroid (ICS) that is administered once daily and is available in 100 mcg and 200 mcg strengths.³

The starting dosage for fluticasone furoate is based upon patients' asthma severity with patients who have not previously been on an ICS starting at 100 mcg once daily. For patients who do not respond to the 100 mcg dose after two weeks of therapy, the dose should be increased to 200 mcg once daily (the highest recommended daily dose). Maximum benefit may not be achieved for up to two weeks or longer after starting treatment.⁴ Administration

of fluticasone furoate requires the patient to fully open the cover of the inhaler and inhale deeply through the mouthpiece. One potential downside of this formulation is that opening and closing the cover (without inhaling the medication) will result in a lost dose that is unable to be recovered.

Approval was based on four confirmatory clinical trials in subjects with asthma aged 12 years and older. These trials evaluated the efficacy and safety of fluticasone furoate, given once daily in the evening, on lung function in subjects who had a diagnosis of asthma for ≥ 12 weeks, were maintained on a stable ICS dose for ≥ 4 weeks, had a pre-bronchodilator FEV₁ of 40-90% (adjusted for ethnicity), and evening reversibility of $\geq 12\%$ and ≥ 200 mL following albuterol/salbutamol inhalation. This last requirement presents a problem of selection bias given that patients with a positive bronchodilator response will very likely show improvement in FEV₁ in such studies. In trials with placebo arms, the treatment groups did not show significant improvements in asthma control and quality of life measures as compared with placebo.

The first trial evaluated fluticasone furoate (FF) 100 mcg once daily over 24 weeks versus placebo in patients.⁵ Fluticasone propionate (FP) 250 mcg was included as an active control. Three hundred forty-three subjects were randomized 1:1:1 to FF 100 mcg once-daily, placebo once-daily, or FP 250 mcg twice-daily. The primary endpoint was change from baseline in pre-dose evening FEV₁ at week 24. Both FF 100 mcg and FP 250 mcg significantly improved pre-dose evening FEV₁ compared to placebo at week 24 [146 mL ($p = 0.009$) and 145 mL ($p = 0.011$), respectively].

The second trial evaluated the combination of fluticasone furoate and vilanterol 100-25 mcg (FF/VI) and FF 100 mcg compared with placebo in 609 patients over a 12 week period.⁶ Co-primary endpoints were change from baseline in

trough FEV₁ and serial (0-24 hours) weighted mean FEV₁ (wmFEV₁). FF/VI significantly improved trough FEV₁ (+172 mL; $p < 0.001$) and serial wmFEV₁ (+302 mL; $p < 0.001$) compared to placebo. FF alone also significantly improved trough FEV₁ (+136 mL; $p = 0.002$) and serial wmFEV₁ (+186 mL; $p = 0.003$). Improvement in FEV₁ with the addition of VI to FF was not found to be significant.

In the third trial, 239 subjects were stratified by baseline FEV₁ and randomized 1:1 to treatment with FF 100 mcg or 200 mcg once daily in the evening.⁷ The primary endpoint was change from baseline trough FEV₁ after 24 weeks. The least squares mean trough FEV₁ improved from baseline by 208 mL with FF 100 mcg and 284 mL with FF 200 mcg at week 24. A numerically greater increase was observed with FF 200 mcg (77 mL; 95% CI: -39 to 192).

In the fourth trial, 586 subjects were randomized to either FF/VI 200-25 mcg, FF 200 mcg, or FP 500 mcg.⁸ Co-primary endpoints were change from baseline trough FEV₁ and serial (0-24 hour) wmFEV₁. FF/VI significantly improved both trough FEV₁ and wmFEV₁ as compared to FF and FP (193 mL and 210 mL respectively; $p < 0.001$ for both). Adverse effects seen in clinical trials include nasopharyngitis, headache, bronchitis, influenza, upper respiratory tract infection, sinusitis, oropharyngeal pain, and pharyngitis.

Fluticasone furoate and vilanterol

On April 30, 2015, the FDA approved fluticasone furoate/vilanterol (Breo[®] Ellipta[®]) for the once-daily treatment of asthma in patients aged 18 years and older. GlaxoSmithKline originally submitted for approval in patients aged 12 years of age and older. The FDA issued a response letter related to the proposed use in patients aged 12 to 17 years, stating that the data submitted did not show adequate risk-benefit to support approval in this patient population. The FDA stated that additional data would be required to further demonstrate the safety and efficacy for these patients.⁹ Despite the lack of FDA approval, FF/VI appears to be well-tolerated in this patient population.

The efficacy and safety of fluticasone furoate and vilanterol (FF/VI) was evaluated in several studies involving subjects 12 years of age and older.¹⁰ One such study evaluated the addition of VI to once-daily FF on the risk of severe asthma exacerbations in patients with uncontrolled asthma. In this study, 2019 subjects aged 12 years and older with asthma and at least one documented exacerbation were randomized to FF/VI 100/25 mcg or FF 100 mcg once-daily in the evening. The primary endpoint was time to

first severe exacerbation. A severe exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days, or inpatient hospitalization, or emergency department visit due to asthma requiring systemic corticosteroids. FF/VI significantly delayed the time to first severe asthma exacerbation relative to FF alone. The adjusted probability of experiencing a severe asthma exacerbation at 52 weeks was 15.9% (95% CI 13.5% to 18.2%) in the FF 100 mcg group and 12.8% (95%CI 10.7 to 14.9%) in the FF/VI 100/25 mcg group. Subjects in the FF/VI and FF groups experienced similar adverse events.

Variations of Existing Formulations

Albuterol sulfate

On April 1, 2015, the FDA approved albuterol sulfate inhalation powder (ProAir[®] RespiClick), a breath-actuated, multi-dose, dry-powder, short-acting beta-agonist (SABA) inhaler. It is approved for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease. The rationale for this product is based on references revealing nearly two-thirds of patients cannot correctly coordinate inhalation and actuation of a metered-dose inhaler.¹¹ Children aged 6 to 11 years were not included in this approval, but could benefit greatly from this formulation.

The recommended dose of ProAir[®] Respiclick is two inhalations every four to six hours. Each actuation delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg albuterol base). Each inhaler supplies 200 doses. In order to deliver the medication, patients only need to breathe in deeply through the mouthpiece. ProAir[®] Respiclick should not be used with a spacer or volume holding chamber.¹²

ProAir[®] Respiclick was studied in two identical 12-week placebo-controlled trials in 316 total subjects 12 years of age and older with asthma.¹² Subjects were randomized to either ProAir[®] Respiclick 180 mcg four times daily or placebo. All patients were maintained on ICS treatment. In Study 1, 44 of 78 patients treated with ProAir[®] Respiclick achieved a 15% increase in FEV₁ within 30 minutes post-dose on Day 1. The median time to onset was 5.7 minutes and median duration of effect, as measured by a 15% increase, was approximately 2 hours. Study 2 showed similar results.

A double-blind, randomized, placebo-controlled, single-dose crossover study evaluated ProAir[®] Respiclick and ProAir[®] HFA in 337 subjects 12 years of age and older with persistent asthma.¹²

ProAir[®] Respiclick had greater efficacy than placebo at administered doses of 90 and 180 mcg. Adverse effects experienced in $\geq 5\%$ of patients treated with ProAir Respiclick for 52 weeks include upper respiratory tract infection, nasopharyngitis, sinusitis, bronchitis, cough, oropharyngeal pain, headache, and pyrexia.

Tiotropium bromide

Tiotropium bromide (Spiriva[®] Respimat[®]) inhalation spray was approved by the FDA for maintenance treatment of asthma in patients 12 years of age and older on September 16, 2015.¹³ The recommended starting dose for tiotropium bromide in children 12 years of age for maintenance treatment of asthma is two inhalations of the 1.25 mcg dose once-daily. The Respimat device differs from the previous Handihaler formulation in that it delivers a dose as a soft mist that has been shown to more effectively disperse small particles to the lower respiratory tract than a dry powder inhaler. The Respimat device, however, requires similar cartridge insertion, priming, and breath coordination as traditional hydrofluoroalkane (HFA) inhalers. To deliver a dose of the medication, patients must turn the base of the inhaler until it clicks, flip open the cap of the mouthpiece, and then simultaneously press the dose release button while inhaling deeply.¹⁴ While this formulation does have the advantage of improved delivery to the site of action, the number of steps involved in the administration of each dose could prove to be problematic for children and/or their caregivers.

Two identical, randomized, controlled trials were conducted in 912 subjects with asthma (mean age 53 years) who were receiving therapy with a LABA and ICS.¹⁵ Subjects were randomly assigned to receive either two puffs of tiotropium 2.5 mcg or matching placebo delivered each morning using a soft-mist inhaler (Respimat) as add-on therapy. The co-primary endpoints for each trial were peak FEV₁ response (within 3 hours after administration of the maintenance and study drugs) and the trough FEV₁ response at week 24. The mean change in peak FEV₁ from baseline at 24 weeks was greater with tiotropium than with placebo in both trials with a difference of 86 ± 34 mL ($p = 0.01$) in trial 1 and 154 ± 32 mL in trial 2 ($p < 0.001$). Trough FEV₁ also improved with a difference of 88 ± 31 mL ($p = 0.01$) and 111 ± 30 mL ($p < 0.001$) respectively.

A randomized, double-blind, placebo-controlled, incomplete crossover study was conducted in adolescents age 12 to 17 years to evaluate the safety and efficacy of three doses of tiotropium as add-on treatment.¹⁶ One hundred and five subjects were randomized 1:1:1:1 to receive tiotropium 5 mcg, 2.5 mcg, 1.25 mcg, or placebo

once-daily in the evening for three four-week periods. Patients also received medium-dose ICS therapy. The primary end point was peak FEV₁, measured three hours post-dose. Peak FEV₁ response for tiotropium 5 mcg was significantly greater than placebo (treatment difference 489 mL; $p = 0.0043$). Adverse events were consistent between groups.

While current approval is only for adolescents aged 12 to 17 years, studies have been conducted in younger children. In a phase II, double-blind, placebo-controlled, incomplete-crossover study, 101 subjects age 6 to 11 years were randomized to receive three out of four of the following treatments: tiotropium 5 mcg, 2.5 mcg, 1.25 mcg, or placebo once-daily in the evening for three four-week periods.¹⁷ Subjects also received medium-dose ICS therapy, with or without a leukotriene modifier. The primary end point was peak FEV₁, measured three hours post-dose. The adjusted mean responses with tiotropium 5 mcg (272 mL; $p < 0.001$) 2.5 mcg (290 mL; $p < 0.001$) and 1.25 mcg (261 mL; $p = 0.0011$) were significantly greater than with placebo (185 mL). The safety and tolerability of all doses of tiotropium were comparable with those of placebo.

A Glimpse into the Future

Beclomethasone Dipropionate

Beclomethasone dipropionate (QVAR[®]) inhalation aerosol was originally approved by the FDA on September 15, 2000 for maintenance treatment of asthma as prophylactic therapy in adults and adolescents 12 years of age and older. Beclomethasone dipropionate is unique in that it is formulated as a solution rather than a suspension with a particle size of about 1 μ m. Its small particle size is better able to penetrate both the large and small airways of the lungs.

In May 2002, approval was extended to children 5 to 11 years of age. On May 23, 2014, the FDA approved the addition of a dose counter to the beclomethasone dipropionate HFA.¹⁸ The recommended starting dose for children 5 to 11 years old is 40 mcg twice daily (max 80 mcg twice daily), regardless of previous asthma control therapy. For patients aged 12 years and older not previously receiving ICS therapy, the starting dose is 40 to 80 mcg twice daily (max 360 mcg twice daily); for patients previously receiving ICS therapy, the starting dose is 40 to 160 mcg twice daily (max 360 mcg twice daily).¹⁹

QVAR[®] (beclomethasone dipropionate) breath actuated inhaler (BAI) began phase III clinical trials in the U.S. in December 2013. Similar in design to the Respiclick inhaler, the BAI would

eliminate the need for the patient to coordinate pressing a dose-release button while simultaneously inhaling deeply. One study will evaluate the efficacy of beclomethasone dipropionate administered via BAI at a dose of 320 mcg or 640 mcg per day compared with placebo in subjects 12 years of age or older with persistent asthma. The primary endpoint is standardized baseline-adjusted trough morning FEV₁ area under the effect curve from time 0 to 6 weeks. The estimated primary completion date is June 2016.²⁰

Another study will evaluate the efficacy and safety of beclomethasone dipropionate at a dose of 80 mcg or 160 mcg per day administered via BAI and MDI compared with placebo in pediatric patients age 4 to 11 with persistent asthma. The primary endpoint is change from baseline in percent predicted trough morning FEV₁ over the 12 week treatment period. The estimated primary completion date is January 2016.²¹ If approved by the FDA, beclomethasone dipropionate BAI will provide yet another therapy for maintenance treatment of asthma that could potentially have a positive impact on compliance and outcomes in children and adolescents with asthma.

The editors would like to thank Dr. W. Gerald Teague for serving as our guest editor this month.

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