

Product Summary for *Arnuity Ellipta*

This information is provided in response to your request for information about Arnuity™ Ellipta® (fluticasone furoate inhalation powder).

SUMMARY

- Important safety information is found in the attached Prescribing Information.

DISEASE BACKGROUND

- Because asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations, persistent asthma is most effectively controlled with daily long-term control medication, specifically, anti-inflammatory therapy.⁽¹⁾
- Inhaled corticosteroids (ICSs) are the preferred treatment option for initiating long-term control therapy.

DESCRIPTION

- *Arnuity Ellipta* is a once-daily ICS delivered from a dry powder, breath-actuated inhaler.⁽²⁾ The dry powder inhaler contains one foil blister strip with each blister containing fluticasone furoate (FF) 100 mcg or FF 200 mcg.
- FF is chemically and pharmacologically distinct from fluticasone propionate (FP).^(3,4) Structurally, FF is characterized by the combination of a furoate ester at the 17 α position of the fluticasone steroid template. Fluticasone furoate exerts activity as an intact molecule, and not as a pro-drug or alternative salt of fluticasone. FF and FP share no common metabolites, and neither compound is metabolized to fluticasone base.
- FF has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is approximately 1.7 times that of FP.⁽²⁾ The clinical relevance of these findings is unknown.

INDICATION

- *Arnuity Ellipta* is an ICS indicated for the once-daily maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. *Arnuity Ellipta* is not indicated for the relief of acute bronchospasm.⁽²⁾

DOSING

- *Arnuity Ellipta* 100 mcg or 200 mcg should be administered as 1 inhalation once daily (QD) by the orally inhaled route.⁽²⁾ Patients should be advised to rinse his/her mouth with water without swallowing after each dose.
- *Arnuity Ellipta* should be used at the same time every day and not more than 1 time every 24 hours.
- The starting dosage for *Arnuity Ellipta* is based upon patients' asthma severity. The usual recommended starting dose for patients not on an ICS is 100 mcg. For other patients, the starting dose should be based on previous asthma drug therapy and disease severity.
- The highest recommended dose is 200 mcg QD.

EFFICACY DATA

- The clinical development program included 3 dose-ranging trials of 8 weeks' duration and 4 confirmatory trials of 3 and 6 months' duration.⁽²⁾
- The primary endpoint for all 4 confirmatory trials was change from baseline in trough forced expiratory volume in one second (FEV₁) at the end of the treatment period. Trials 2 and 4 also had a co-primary endpoint of weighted mean (wm) serial FEV₁ at 0-24 hours after the final dose of study medication.
- Trial 1 (N = 343) was a 24-week trial that evaluated FF versus placebo for the treatment of persistent asthma uncontrolled by low-to-medium dose ICS (FP 100 to 500 mcg daily or equivalent).⁽⁵⁾ Subjects were evaluated on FF 100 mcg QD, FP 250 mcg twice daily (BID), or placebo. FF and FP showed significant improvement in the primary endpoint (treatment difference from placebo 146 mL and 145 mL, respectively).⁽²⁾ No statistical comparison was made between the FF and FP arms.⁽⁵⁾
- Trial 2 (N = 609) was a 12-week trial that enrolled subjects on a stable low-to-medium dose ICS (FP 200 to 500 mcg/daily or equivalent) with or without a LABA, and evaluated FF 100 mcg QD, FF/vilanterol (VI) 100/25 mcg QD, and placebo.⁽⁶⁾ If LABA was used prior to screening, it was discontinued during the 4-week run-in period. Compared with placebo, both FF/VI and FF showed statistically significant improvements in the co-primary endpoints. At Week 12, the change from baseline in trough FEV₁ compared with placebo was 136 mL and 172 mL for FF and FF/VI respectively. The change from baseline in wm serial FEV₁ at 0-24 hours after the final dose of study medication for FF and FF/VI compared to placebo was 186 mL and 302 mL respectively.
- Subjects in Trial 1 and 2 receiving FF 100 mcg QD had a greater improvement from baseline in the powered secondary endpoint of percentage of 24-hour periods without need of beta₂-agonist rescue medications than subjects receiving placebo.^(2,5,6)
- Trial 3 (N = 219) was a 24-week trial which evaluated FF 100 mcg and 200 mcg once daily in subjects \geq 12 years old with persistent asthma who were on medium-to-high dose ICS (FP greater than 250 to 1,000 mcg/day or equivalent) with or without a LABA.⁽⁷⁾ If LABA was used prior to screening, it was discontinued during the 4-week run-in period. This was a descriptive study with no inferential statistical analysis planned or performed. After 24 weeks of treatment, the primary endpoint was 208 mL and 284 mL for FF 100 mcg and 200 mcg respectively (treatment difference between the two strengths 77 mL; 95% CI: -39, 192).
- Trial 4 (N = 586) was a 24-week trial which evaluated FF/VI 200/25 mcg QD, FF 200 mcg QD, and FP 500 mcg BID in subjects \geq 12 years old who were symptomatic on a medium-to-high dose ICS with or without a LABA.⁽⁸⁾ If LABA was used prior to screening, it was discontinued during the 4-week run-in period. Additionally, this trial included a non-inferiority test for FF 200 mcg QD and FP 500 mcg BID for the change from baseline in trough FEV₁. At Week 24, the change from baseline in trough FEV₁ was 201 mL and 183 mL for FF and FP respectively (treatment difference of 18 mL, 95 CI: -66, 102).⁽²⁾ Non-inferiority was demonstrated for the comparison between FF 200 mcg QD and FP 500 mcg BID.⁽⁸⁾ The change from baseline in wm serial FEV₁ at 0-24 hours after the final dose of study medication was 328 mL and 258 mL for FF and FP respectively.

CONTRAINDICATIONS

- *Arnuity Ellipta* is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.⁽²⁾
- *Arnuity Ellipta* is also contraindicated in patients with known severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to any other ingredients of *Arnuity Ellipta*.

WARNINGS AND PRECAUTIONS

- Localized infections: *Candida albicans* infection of the mouth and throat may occur.⁽²⁾ Monitor patients periodically. Advise the patient to rinse his/her mouth with water, without swallowing after inhalation.
- Deterioration of asthma and acute episodes: Do not use for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma.
- Immunosuppression: Potential worsening of existing tuberculosis, fungal, bacterial, viral, parasitic infections or ocular herpes simplex. Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients.
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from systemic corticosteroids. Wean patients slowly from systemic corticosteroids if transferring to *Arnuity Ellipta*.
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue *Arnuity Ellipta* slowly.
- Drug Interactions with strong cytochrome P450 3A4 inhibitors: Caution should be exercised when considering the co-administration of *Arnuity Ellipta* with long-term ketoconazole and other known strong CYP3A4 inhibitors because increased systemic corticosteroid adverse effects may occur.⁽²⁾
- Paradoxical bronchospasm: Discontinue *Arnuity Ellipta* and institute alternative therapy if paradoxical bronchospasm occurs.
- Hypersensitivity Reactions, Including Anaphylaxis: Hypersensitivity reactions such as urticaria, flushing, allergic dermatitis, and bronchospasm may occur after administration of *Arnuity Ellipta*. Discontinue *Arnuity Ellipta* if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use *Arnuity Ellipta*.⁽²⁾
- Reduction in Bone Mineral Density: Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content.
- Effect on Growth: Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. Monitor growth of children and adolescent patients.
- Glaucoma and Cataracts: Close monitoring for glaucoma and cataracts is warranted.

ADVERSE EVENTS

- The safety of *Arnuity Ellipta* was evaluated in 10 double-blind, parallel-group, controlled trials (7 with placebo) of 8 to 76 weeks' duration, which enrolled 6219 subjects, with asthma.⁽²⁾ Doses of FF studied ranged from 25 to 800 mcg. FF 100 mcg was studied in 1663 subjects, and FF 200 mcg was studied in 608 subjects.
- The most common adverse reactions (reported in greater than or equal to 5% of subjects) across the 10 trials were: upper respiratory tract infection, nasopharyngitis, headache, and bronchitis.
- In one 52-week trial evaluating FF 100 mcg (n = 201) and FF 200 mcg (n = 202), each in combination with a LABA, subjects experienced adverse reactions similar to what was reported in the confirmatory trials. Additional adverse events occurring in $\geq 3\%$ of the subjects taking FF 100 mcg or FF 200 mcg with LABA included pyrexia, extrasystoles, upper abdominal pain, respiratory tract infection, diarrhea, and allergic rhinitis.
- In a second long-term trial, subjects received FF 100 mcg (n = 1010) and were followed from 24 up-to 76 weeks. Subjects were required to have a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or inpatient hospitalization for the treatment of asthma within the previous 12 months. In addition to the adverse reactions reported in the confirmatory trials, reactions occurring in $\geq 3\%$ of the subjects taking FF 100 mcg included allergic rhinitis, nasal congestion, and arthralgia.

This information is provided in response to your request. GSK requests that the recipient of this information only share the contents with the Pharmacy & Therapeutics (P & T) Committee members for the purposes of making evidence-based decisions regarding formulary inclusion.

REFERENCE(S)

1. National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. NHLBI 2007; [Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm](http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm).*
2. GlaxoSmithKline Local Label. *
3. Salter M, Biggadike K, Matthews J, et al. Pharmacological properties of the enhanced-affinity glucocorticoid fluticasone furoate in vitro and in an in vivo model of respiratory inflammatory disease. *Am J Physiol Lung Cell Mol Physiol* 2007;293:L660-L667.*
4. Rossios C, To Y, To M, et al. Long-acting fluticasone furoate has a superior pharmacological profile to fluticasone propionate in human respiratory cells. *Eur. J. Pharmacol* 2011;(670):244-251.*
5. Lötval J, Bleecker ER, Busse WW, et al. Efficacy and safety of fluticasone furoate 100 mcg once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomised . *Respir Med* 2014;108(1):41-49. (FFA112059).*
6. Bleecker ER, Lötval J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. *J Allergy Clin Immunol Pract* 2014;2(5):553-561. (HZA106827).*
7. Woodcock A, Lötval J, Busse WW, et al. Efficacy and safety of fluticasone furoate 100 mcg and 200 mcg once daily in the treatment of moderate-severe asthma in adults and adolescents: a 24-week randomised study. *BMC Pulm Med* 2014;14:113. (FFA114496).*
8. O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. *Eur Respir J* 2014;43(3):773-782 (HZA106829).*