HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARNUITY ELLIPTA safely and effectively. See full prescribing information for ARNUITY ELLIPTA.

ARNUITY ELLIPTA (fluticasone furoate inhalation powder) 100 mcg
ARNUITY ELLIPTA (fluticasone furoate inhalation powder) 200 mcg
FOR ORAL INHALATION
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------

ARNUITY ELLIPTA is a corticosteroid indicated for:

- once-daily maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. (1.1)

Important limitation:

- Not indicated for relief of acute bronchospasm. (1.1, 5.2)

---------- DOSAGE AND ADMINISTRATION ----------

For oral inhalation only. (2.1)

- Starting dosage is based on prior asthma therapy and disease severity. (2.2)
- Treatment of asthma in patients aged 12 years and older: 1 inhalation of ARNUITY ELLIPTA 100 mcg or ARNUITY ELLIPTA 200 mcg once daily. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Inhalation powder containing 100 or 200 mcg of fluticasone furoate per actuation. (3)

----------CONTRAINDICATIONS----------

- Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. (4.1)
- Severe hypersensitivity to milk proteins or any ingredients of ARNUITY ELLIPTA. (4.2)

---------- WARNINGS AND PRECAUTIONS----------

- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation. (5.1)
- Deterioration of asthma and acute episodes: Do not use for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma. (5.2)
- 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. (5.3)
- 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. (5.4)
- 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. (5.5)
- Paradoxical bronchospasm: Discontinue ARNUITY ELLIPTA and institute alternative therapy if paradoxical bronchospasm occurs. (5.7)
- Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content. (5.9)
- Monitor growth of adolescent patients. (5.10)
- Close monitoring for glaucoma and cataracts is warranted. (5.11)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (reported in greater than or equal to 5% of subjects) are:

- upper respiratory tract infection, nasopharyngitis, headache, and bronchitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Strong cytochrome P450 3A4 inhibitors (e.g., ketoconazole): Use with caution. May cause systemic corticosteroid effects. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

Hepatic impairment: Fluticasone furoate exposure may increase in patients with moderate or severe impairment. Monitor for systemic corticosteroid effects. (8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

1.1 Treatment of Asthma

ARNUITY™ ELLIPTA® is indicated for the once-daily maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older.

Important Limitation of Use: ARNUITY ELLIPTA is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

2.1 General

ARNUITY ELLIPTA should be administered only by the orally inhaled route *[see Instructions for Use in the Patient Information leaflet]*. Advise the patient to rinse his/her mouth with water without swallowing after each dose.

2.2 Dosing

ARNUITY ELLIPTA should be administered as 1 inhalation once daily by the orally inhaled route. ARNUITY ELLIPTA should be used at the same time every day. Do not use ARNUITY ELLIPTA 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 inhaled corticosteroid is 100 mcg. For other patients, the starting dose should be based on previous asthma drug therapy and disease severity. For patients who do not respond to ARNUITY ELLIPTA 100 mcg after 2 weeks of therapy, replacement with ARNUITY ELLIPTA 200 mcg may provide additional asthma control.

If a dosage regimen of ARNUITY ELLIPTA fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options, e.g., replacing the current strength of ARNUITY ELLIPTA with a higher strength, initiating an inhaled corticosteroid and long-acting $beta_2$-agonist (LABA) combination product, or initiating oral corticosteroids, should be considered.

The highest recommended daily dose is 200 mcg. If symptoms arise between doses, an inhaled short-acting $beta_2$-agonist should be used for immediate relief.

The maximum benefit may not be achieved for up to 2 weeks or longer after starting treatment. Individual patients may experience a variable time to onset and degree of symptom relief.

After asthma stability has been achieved, it is desirable to titrate to the lowest effective dosage to help reduce the possibility of side effects.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Powder. Disposable light grey and orange plastic inhaler containing a foil blister strip of powder intended for oral inhalation only. Each blister contains fluticasone furoate 100 or 200 mcg.

4 CONTRAINDICATIONS

4.1 Status Asthmaticus

ARNUITY ELLIPTA is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required *[see Warnings and Precautions (5.2)]*.

4.2 Hypersensitivity

ARNUITY ELLIPTA is contraindicated in patients with known severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to fluticasone furoate or any of the excipients *[see Warnings and Precautions (5.8), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Local Effects of Inhaled Corticosteroids

In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with ARNUITY ELLIPTA. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with ARNUITY ELLIPTA continues, but at times therapy with ARNUITY ELLIPTA may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.2 Acute Asthma Episodes

ARNUITY ELLIPTA is not indicated for the relief of acute symptoms, i.e., as rescue therapy for treatment of acute episodes of bronchospasm. An inhaled, short-acting $beta_2$-agonist, not ARNUITY ELLIPTA, should be used to relieve acute symptoms such as shortness of breath. When prescribing ARNUITY ELLIPTA, the physician must provide the patient with an inhaled, short-acting $beta_2$-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular once-daily use of ARNUITY ELLIPTA. Instruct patients to contact their physicians immediately if episodes of asthma not responsive to bronchodilators occur during the course of treatment with ARNUITY ELLIPTA. During such episodes, patients may require therapy with oral corticosteroids.

5.3 Immunosuppression

Persons using drugs that suppress the immune system are more susceptible to infections than healthy individuals.

Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such patients who have not had these diseases or who have not been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of

developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.4 Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although ARNUITY ELLIPTA may improve control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring systemic corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to ARNUITY ELLIPTA. Lung function (forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [AM PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of systemic corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to ARNUITY ELLIPTA may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression), despite maintenance or even improvement of respiratory function.

5.5 Hypercorticism and Adrenal Suppression

ARNUITY ELLIPTA will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since ARNUITY ELLIPTA is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of ARNUITY ELLIPTA in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of significant systemic absorption of inhaled corticosteroids, patients treated with ARNUITY ELLIPTA should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when fluticasone furoate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of ARNUITY ELLIPTA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

5.6 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of ARNUITY ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

5.7 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medicines, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with ARNUITY ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ARNUITY ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.

5.8 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 *[see Contraindications (4.2)]*.

5.9 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term outcomes, such as fracture, is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids), should be monitored and treated with established standards of care.

5.10 Effect on Growth

Orally inhaled corticosteroids, including ARNUITY ELLIPTA, may cause a reduction in growth velocity when administered to children and adolescents. Monitor the growth of children and adolescents receiving ARNUITY ELLIPTA routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including ARNUITY ELLIPTA, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Use in Specific Populations (8.4)]*.

5.11 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.1)]*
- Immunosuppression *[see Warnings and Precautions (5.3)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.5)]*
- Reduction in BMD *[see Warnings and Precautions (5.9)]*
- Growth effects in pediatrics *[see Warnings and Precautions (5.10)]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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 6,219 subjects with asthma. Doses of fluticasone furoate studied ranged from 25 to 800 mcg.

ARNUITY ELLIPTA 100 mcg was studied in 1,663 subjects, and ARNUITY ELLIPTA 200 mcg was studied in 608 subjects. Subject ages ranged from 12 to 84 years, 65% were female, and 75% were Caucasian.

In these trials, the proportion of subjects who discontinued study treatment early due to adverse reactions was 2% for subjects treated with both ARNUITY ELLIPTA 100 mcg and ARNUITY ELLIPTA 200 mcg and less than or equal to 1% for placebo-treated subjects. Serious

adverse events, whether considered drug-related or not by the investigators, that occurred in more than 1 subject and in a greater percentage of subjects treated with ARNUITY ELLIPTA than placebo included hypertension, abscess, breast cancer, traumatic limb amputation, subarachnoid hemorrhage, and intervertebral disc protrusion; all events occurred at rates less than or equal to 1%.

The incidence of adverse reactions associated with ARNUITY ELLIPTA 100 mcg is shown in Table 1 and is based on one 24-week trial (Trial 1) in adolescent and adult subjects with asthma.

Table 1. Adverse Reactions with ARNUITY ELLIPTA 100 mcg with Greater than or Equal to 3% Incidence and More Common than Placebo (Trial 1, Intent-to-Treat Population)

Adverse Event	ARNUITY ELLIPTA 100 mcg n = 114 %	Placebo n = 115 %
Bronchitis	7	6
Headache	6	4
Nasopharyngitis	8	5
Upper respiratory tract infection	6	5
Pharyngitis	4	3
Sinusitis	4	<1
Oropharyngeal pain	3	0
Toothache	3	<1
Gastroenteritis viral	3	0
Oral candidiasis	3	0
Oropharyngeal candidiasis	3	0

The incidence of adverse reactions associated with ARNUITY ELLIPTA 200 mcg is shown in Table 2 and is based on one 24-week trial (Trial 3) in adolescent and adult subjects with asthma. This trial did not have a placebo arm.

Table 2. Adverse Reactions with ARNUITY ELLIPTA 200 mcg with Greater than or Equal to 3% Incidence (Trial 3, Safety Population)

Adverse Event	ARNUITY ELLIPTA 200 mcg n = 119 %	ARNUITY ELLIPTA 100 mcg n = 119 %
Nasopharyngitis	13	12
Headache	13	10
Bronchitis	7	12
Influenza	7	4
Upper respiratory tract infection	6	2
Sinusitis	4	7
Oropharyngeal pain	4	3
Pharyngitis	3	6
Back pain	3	3
Dysphonia	3	2
Oral candidiasis	3	<1
Procedural pain	3	<1
Rhinitis	3	<1
Throat irritation	3	<1
Abdominal pain	3	0
Cough	3	0

Adverse reactions observed in the other trials were consistent with those described in Tables 1 and 2.

Long-Term Safety: Long-term safety data are based on 2 trials in adolescent and adult subjects with asthma. In one 52-week trial, subjects received fluticasone furoate 100 mcg (n = 201) or fluticasone furoate 200 mcg (n = 202) in combination with a LABA. Subjects had a mean age of 39 years (adolescents made up 16% of the population), 63% were female, and 67% were Caucasian. In addition to the events shown in Table 1 and Table 2, adverse events occurring in greater than or equal to 3% of the subjects treated with fluticasone furoate 100 mcg or fluticasone furoate 200 mcg, in combination with a LABA, included pyrexia, extrasystoles, upper abdominal pain, respiratory tract infection, diarrhea, and allergic rhinitis.

In a second 24- to 76-week trial, subjects received fluticasone furoate 100 mcg (n = 1,010). Subjects participating in this trial had a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma within the previous 12 months. Subjects had a mean age of 42 years (adolescents made up 14% of the population), 67% were female, and 73% were Caucasian. In addition to the events shown in Table 1 and Table 2, adverse events occurring in

greater than or equal to 3% of subjects treated with fluticasone furoate 100 mcg for up to 76 weeks included allergic rhinitis, nasal congestion, and arthralgia.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate. Caution should be exercised when considering the coadministration of ARNUITY ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with ARNUITY ELLIPTA in pregnant women. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, ARNUITY ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking ARNUITY ELLIPTA.

There were no teratogenic effects in rats and rabbits at approximately 4 times and equal to, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m^2 basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately equal to the MRHDID in adults (on a mcg/m^2 basis at maternal doses up to 27 mcg/kg/day).

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ARNUITY ELLIPTA during labor and delivery.

8.3 Nursing Mothers

It is not known whether fluticasone furoate is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Since there are no data from controlled trials on the use of ARNUITY ELLIPTA by nursing mothers, caution should be exercised when it is administered to a nursing woman.

8.4 Pediatric Use

The safety and efficacy in pediatric patients younger than 12 years have not been established.

Effects on Growth: Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from use of corticosteroids, including inhaled corticosteroids. The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone furoate, on final adult height are not known.

Controlled clinical trials have shown that inhaled corticosteroids may cause a reduction in growth in children. In these trials, the mean reduction in growth velocity was approximately 1 cm/year (range: 0.3 to 1.8 cm/year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in children than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of children and adolescents receiving orally inhaled corticosteroids, including ARNUITY ELLIPTA, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including ARNUITY ELLIPTA, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A randomized, double-blind, parallel-group, multicenter, 1-year, placebo-controlled trial evaluated the effect of once-daily treatment with 110 mcg of fluticasone furoate in the nasal spray formulation on growth velocity assessed by stadiometry. The systemic exposure of fluticasone furoate in this trial is lower than that of ARNUITY ELLIPTA. The subjects were 474 prepubescent children (girls aged 5 to 7.5 years and boys aged 5 to 8.5 years). Mean growth velocity over the 52-week treatment period was lower in the subjects receiving fluticasone furoate nasal spray (5.19 cm/year) compared with placebo (5.46 cm/year). The mean reduction in growth velocity was 0.27 cm/year (95% CI: 0.06, 0.48) *[see Warnings and Precautions (5.10)]*.

8.5 Geriatric Use

For the 4 confirmatory trials, 71 subjects were aged 65 and older (56 of which were treated with ARNUITY ELLIPTA) and 5 were aged 75 and older (1 of which was treated with ARNUITY ELLIPTA) *[see Clinical Studies (14.2)]*. Based on available data, no adjustment of the dosage of ARNUITY ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of ARNUITY ELLIPTA did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of

concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Use ARNUITY ELLIPTA with caution in patients with moderate or severe hepatic impairment. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

There were no significant increases in fluticasone furoate exposure in subjects with severe renal impairment (CrCl less than 30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

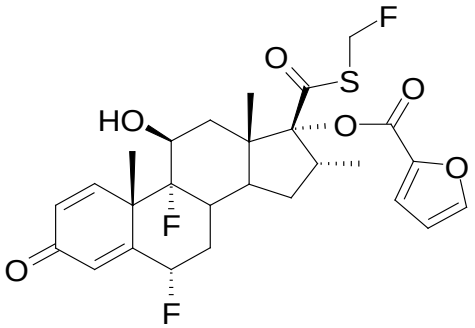
10 OVERDOSAGE

No human overdosage data have been reported for ARNUITY ELLIPTA. The potential for acute toxic corticosteroid effects following overdosage with ARNUITY ELLIPTA is low. Because of low systemic bioavailability (13.9%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.5)]*.

Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

11 DESCRIPTION

The active component of ARNUITY ELLIPTA is fluticasone furoate, a synthetic trifluorinated corticosteroid having the chemical name (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoro-methyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furancarboxylate and the following chemical structure:



Fluticasone furoate is a white powder with a molecular weight of 538.6, and the empirical formula is $C_{27}H_{29}F_3O_6S$. It is practically insoluble in water.

ARNUITY ELLIPTA is a light grey and orange plastic inhaler containing a foil blister strip. Each blister on the strip contains a white powder mix of micronized fluticasone furoate (100 or 200 mcg) and lactose monohydrate (12.4 or 12.3 mg) for a total powder mix of 12.5 mg per blister. The lactose monohydrate contains milk proteins. After the inhaler is activated, the

powder within the blister is exposed and ready for dispersion into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, ARNUITY ELLIPTA 100 mcg and ARNUITY ELLIPTA 200 mcg deliver 90 and 182 mcg, respectively, of fluticasone furoate per blister when tested at a flow rate of 60 L/min for 4 seconds.

In adult subjects with asthma and a mean FEV_1 of 2.55 L/sec (range: 1.63 to 3.97 L/sec), mean peak inspiratory flow through the ELLIPTA inhaler was 103.2 L/min (range: 71.2 to 133.1 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fluticasone furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone furoate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times that of fluticasone propionate. The clinical relevance of these findings is unknown.

The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Though effective for the treatment of asthma, corticosteroids may not affect symptoms immediately. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.

Trials in subjects with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of orally inhaled fluticasone furoate. This is explained by a combination of a relatively high local anti-inflammatory effect, negligible oral systemic bioavailability (approximately 1.3%), and the minimal pharmacological activity of the metabolites detected in man.

12.2 Pharmacodynamics

The pharmacodynamics of fluticasone furoate were characterized in trials of fluticasone furoate given as a single component and also in trials of fluticasone furoate given in combination with vilanterol.

HPA Axis Effects: *Healthy Subjects:* Inhaled fluticasone furoate at repeat doses up to 400 mcg was not associated with statistically significant decreases in serum or urinary cortisol in healthy subjects. Decreases in serum and urine cortisol levels were observed at fluticasone furoate exposures several-fold higher than exposures observed at the therapeutic dose.

Subjects with Asthma: A randomized, double-blind, parallel-group trial in 185 subjects with asthma showed no difference between once-daily treatment with fluticasone furoate/vilanterol 100 mcg/25 mcg or fluticasone furoate/vilanterol 200 mcg/25 mcg compared with placebo on serum cortisol weighted mean (0 to 24 hours), serum cortisol $AUC_{(0-24)}$, and 24-hour urinary cortisol after 6 weeks of treatment, whereas prednisolone 10 mg given once daily for 7 days resulted in significant cortisol suppression.

Cardiac Effects: A QT/QTc trial did not demonstrate an effect of fluticasone furoate administration on the QTc interval. The effect of a single dose of 4,000 mcg of orally inhaled fluticasone furoate on the QTc interval was evaluated over 24 hours in 40 healthy male and female subjects in a placebo- and positive-controlled (a single dose of 400 mg oral moxifloxacin) cross-over trial. The QTcF maximal mean change from baseline following fluticasone furoate was similar to that observed with placebo with a treatment difference of 0.788 msec (90% CI: -1.802, 3.378). In contrast, moxifloxacin given as a 400-mg tablet resulted in prolongation of the QTcF maximal mean change from baseline compared with placebo with a treatment difference of 9.929 msec (90% CI: 7.339, 12.520).

12.3 Pharmacokinetics

The pharmacokinetics of fluticasone furoate were characterized in trials of fluticasone furoate given as a single component and also in trials of fluticasone furoate given in combination with vilanterol. Linear pharmacokinetics were observed for fluticasone furoate (200 to 800 mcg). On repeated once-daily inhalation administration, steady state of fluticasone furoate plasma concentration was achieved after 6 days, and the accumulation was up to 2.6-fold as compared with single dose.

Absorption: Fluticasone furoate plasma levels may not predict therapeutic effect. Peak plasma concentrations are reached within 0.5 to 1 hour. Absolute bioavailability of fluticasone furoate when administrated by inhalation was 13.9%, primarily due to absorption of the inhaled portion of the dose delivered to the lung. Oral bioavailability from the swallowed portion of the dose is low (approximately 1.3%) due to extensive first-pass metabolism. Systemic exposure (AUC) in subjects with asthma was 26% lower than observed in healthy subjects.

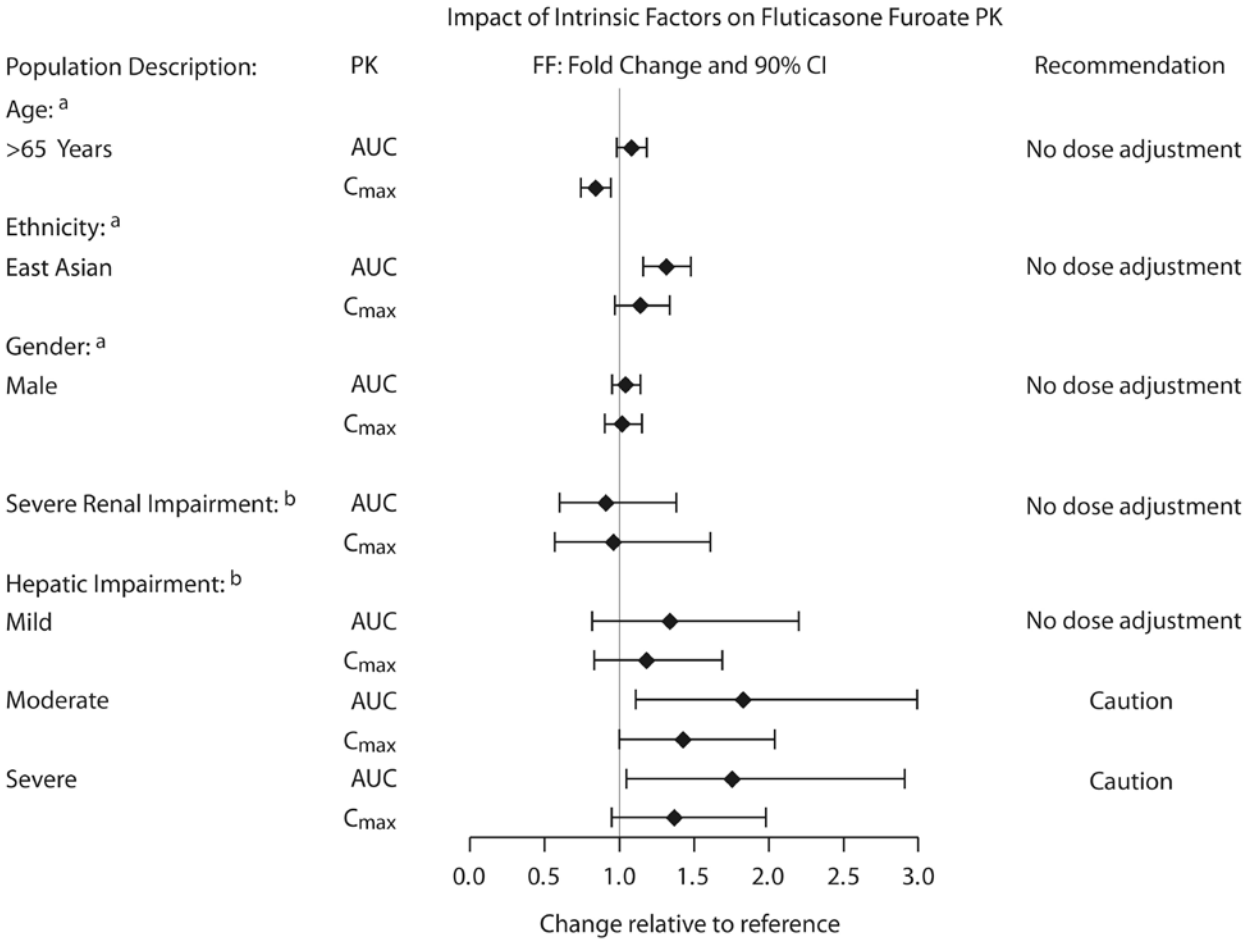
Distribution: Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 661 L. Binding of fluticasone furoate to human plasma proteins was high (99.6%).

Metabolism: Fluticasone furoate is cleared from systemic circulation principally by hepatic metabolism via CYP3A4 to metabolites with significantly reduced corticosteroid activity. There was no in vivo evidence for cleavage of the furoate moiety resulting in the formation of fluticasone.

Elimination: Fluticasone furoate and its metabolites are eliminated primarily in the feces, accounting for approximately 101% and 90% of the orally and intravenously administered doses, respectively. Urinary excretion accounted for approximately 1% and 2% of the orally and intravenously administered doses, respectively. Following repeat-dose inhaled administration, the plasma elimination phase half-life averaged 24 hours.

Special Populations: The effect of renal and hepatic impairment and other intrinsic factors on the pharmacokinetics of fluticasone furoate is shown in Figure 1.

Figure 1. Impact of Intrinsic Factors on the Pharmacokinetics (PK) of Fluticasone Furoate (FF)



[a] Age, gender, and ethnicity comparison for ARNUITY ELLIPTA in subjects with asthma.

[b] Renal groups (fluticasone furoate/vilanterol 200 mcg/25 mcg) and hepatic groups (fluticasone furoate/vilanterol 200 mcg/25 mcg or fluticasone furoate/vilanterol 100 mcg/12.5 mcg) compared with healthy control group.

Race: Systemic exposure ($AUC_{(0-24)}$) to inhaled fluticasone furoate 200 mcg was 27% to 49% higher in healthy subjects of Japanese, Korean, and Chinese heritage compared with Caucasian subjects. Similar differences were observed for subjects with asthma (Figure 1). There is no evidence that this higher exposure to fluticasone furoate results in clinically relevant effects on urinary cortisol excretion or on efficacy in these racial groups.

Hepatic Impairment: Following repeat dosing of fluticasone furoate/vilanterol 200 mcg/25 mcg (100 mcg/12.5 mcg in the severe impairment group) for 7 days, fluticasone

furoate systemic exposure (AUC) increased 34%, 83%, and 75% in subjects with mild, moderate, and severe hepatic impairment, respectively, compared with healthy subjects (see Figure 1).

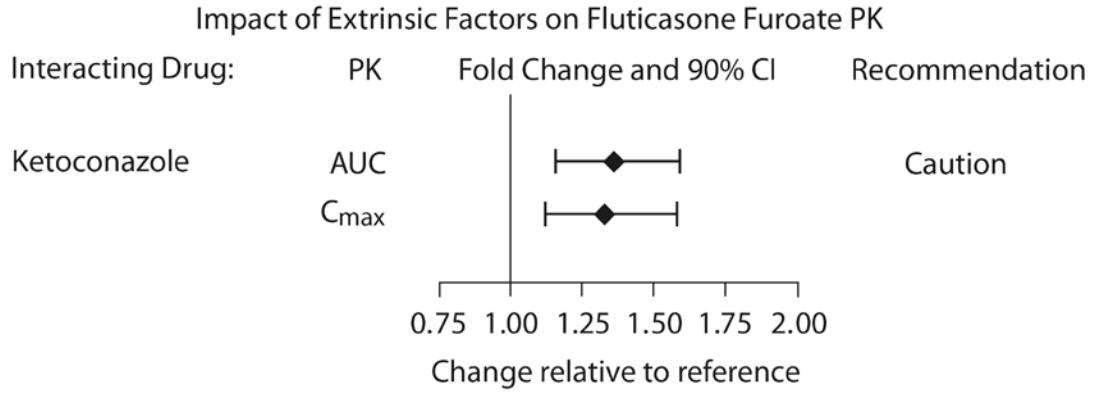
In subjects with moderate hepatic impairment receiving fluticasone furoate/vilanterol 200 mcg/25 mcg, mean serum cortisol (0 to 24 hours) was reduced by 34% (90% CI: 11%, 51%) compared with healthy subjects. In subjects with severe hepatic impairment receiving fluticasone furoate/vilanterol 100 mcg/12.5 mcg, mean serum cortisol (0 to 24 hours) was increased by 14% (90% CI: -16%, 55%) compared with healthy subjects. Patients with moderate to severe hepatic disease should be closely monitored.

Renal Impairment: Fluticasone furoate systemic exposure was not increased in subjects with severe renal impairment compared with healthy subjects (see Figure 1). There was no evidence of greater corticosteroid class-related systemic effects (assessed by serum cortisol) in subjects with severe renal impairment compared with healthy subjects.

Drug Interactions: The potential for fluticasone furoate to inhibit or induce metabolic enzymes and transporter systems is negligible at low inhalation doses.

Inhibitors of Cytochrome P450 3A4: The exposure (AUC) of fluticasone furoate was 36% higher after single and repeated doses when coadministered with ketoconazole 400 mg compared with placebo (see Figure 2). The increase in fluticasone furoate exposure was associated with a 27% reduction in weighted mean serum cortisol (0 to 24 hours).

Figure 2. Impact of Coadministered Ketoconazole[a] on the Pharmacokinetics (PK) of Fluticasone Furoate



[a] Compared with placebo group.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone furoate produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 9 and 19 mcg/kg/day, respectively (less than the MRHDID in adults on a mcg/m^2 basis).

Fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronucleus test in rats.

No evidence of impairment of fertility was observed in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately equal to and 4 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

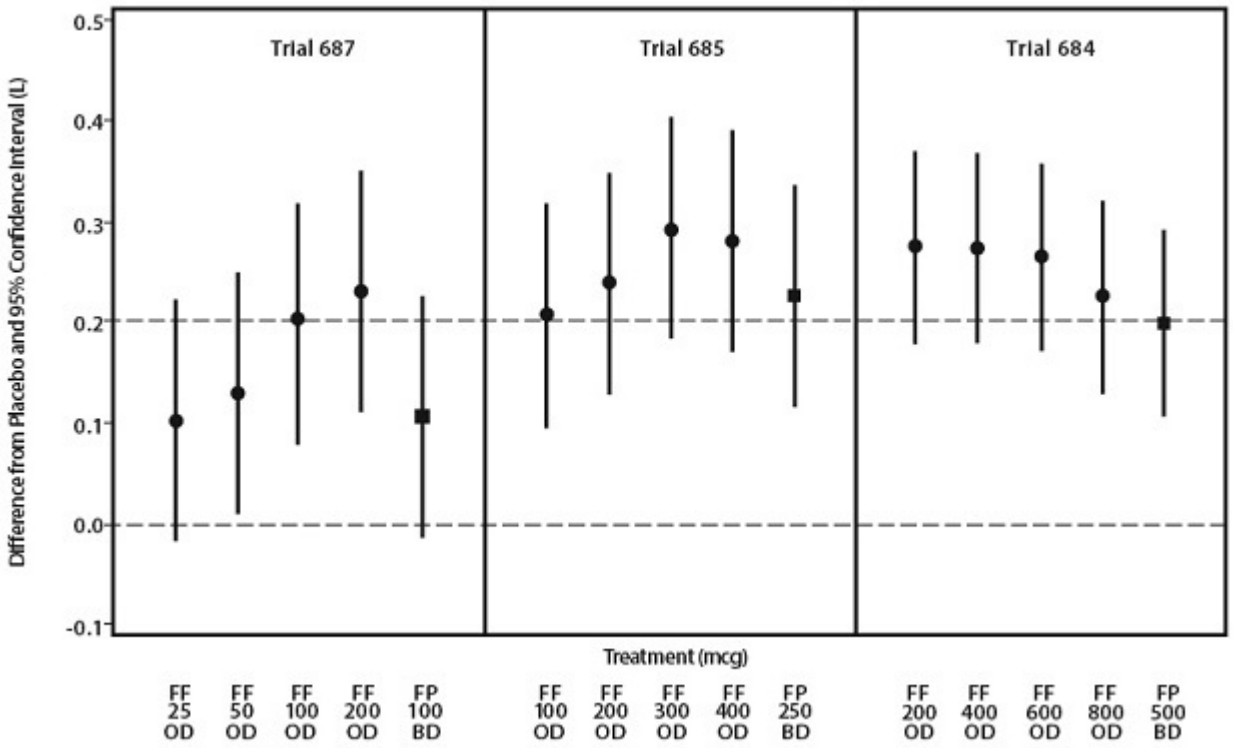
14 CLINICAL STUDIES

The safety and efficacy of ARNUITY ELLIPTA were evaluated in 3,611 subjects with asthma. The development program included 4 confirmatory trials of 3 and 6 months' duration and 3 dose-ranging trials of 8 weeks' duration. The efficacy of ARNUITY ELLIPTA is based primarily on the dose-ranging trials and the confirmatory trials described below.

14.1 Dose-Ranging Trials

Eight doses of fluticasone furoate ranging from 25 to 800 mcg once daily were evaluated in 3 randomized, double-blind, placebo-controlled, 8-week trials in subjects with asthma. Across the 3 trials, subjects were uncontrolled at baseline on treatments of short-acting $beta_2$-agonist and/or non-inhaled corticosteroid controller medications (Trial 687), low-dose inhaled corticosteroid (Trial 685), or medium doses of inhaled corticosteroid (Trial 684). The trials in Figure 3 were dose-ranging trials of ARNUITY ELLIPTA not designed to provide comparative effectiveness data and should not be interpreted as evidence of superiority/inferiority to fluticasone propionate. A dose-related increase in trough FEV_1 at Week 8 was seen for doses from 25 to 200 mcg with no consistent additional benefit for doses above 200 mcg as seen in Figure 3. To evaluate dosing frequency, a separate trial compared fluticasone furoate 200 mcg once daily, fluticasone furoate 100 mcg twice daily, fluticasone propionate 100 mcg twice daily, and fluticasone propionate 200 mcg once daily. The results supported the selection of the once-daily dosing frequency.

Figure 3. Dose-Ranging Trials



FF = Fluticasone furoate.
FP = Fluticasone propionate.
OD = Once daily.
BD = Twice daily.

14.2 Confirmatory Trials

The clinical development program for ARNUITY ELLIPTA included 4 confirmatory trials in adolescent and adult subjects aged 12 years and older with asthma. The trials were designed to evaluate the safety and efficacy of ARNUITY ELLIPTA given once daily in the evening on lung function in subjects who were not controlled on their current treatments of inhaled corticosteroids, or combination therapy consisting of an inhaled corticosteroid plus a LABA. Study treatments were delivered as inhalation powders. The primary endpoint in all trials was change from baseline in evening trough FEV_1 measured approximately 24 hours after the final dose of study medication. Trough FEV_1 (assessed at approximately 24 hours after the previous dose) was also assessed at clinic visits throughout the trials. Trials 2 and 4 had a co-primary endpoint of change from baseline in weighted mean serial FEV_1 measured after the final dose of study medication at 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23, and 24 hours post-dose.

Clinical Trials with ARNUITY ELLIPTA 100 mcg: Trial 1 was a 24-week trial that evaluated the efficacy of ARNUITY ELLIPTA 100 mcg compared with placebo on lung function in subjects with asthma. Inhaled fluticasone propionate 250 mcg twice daily was

included as an active control. Of the 343 subjects, 59% were female and 79% were Caucasian. The mean age was 41 years. The trial included a 4-week run-in period during which the subjects were symptomatic while taking their usual low- to mid-dose inhaled corticosteroid therapy (i.e., fluticasone propionate 100 to 500 mcg daily or equivalent). Mean baseline percent predicted FEV_1 was approximately 73% overall and was similar across the 3 treatment groups. Thirty-five percent of subjects on placebo and 19% of subjects on ARNUITY ELLIPTA 100 mcg failed to complete the 24-week trial.

The change in trough FEV_1 from baseline to Week 24, or the last available on-treatment visit prior to Week 24, was assessed to evaluate the efficacy of ARNUITY ELLIPTA 100 mcg. The mean change from baseline in trough FEV_1 was greater among subjects receiving ARNUITY ELLIPTA 100 mcg than among those receiving placebo (mean treatment difference from placebo 146 mL; 95% CI: 36, 257) as shown in Table 3.

Table 3. Change from Baseline in Trough FEV_1 (mL) at Week 24 – Trial 1

Trough FEV_1 (Week 24)	**Placebo (n = 113)**	**ARNUITY ELLIPTA 100 mcg (n = 111)**	**Fluticasone Propionate 250 mcg Twice Daily (n = 107)**
Least squares mean	2,372	2,519	2,517
Least squares mean change (SE)	15 (39.4)	161 (39.8)	159 (40.6)
Column vs. Placebo			
Difference	---	146	145
95% CI	---	36, 257	33, 257
P value	---	0.009	0.011

Trial 2 was a 12-week trial that evaluated the efficacy of ARNUITY ELLIPTA 100 mcg on lung function in subjects with asthma compared with placebo. The combination of fluticasone furoate 100 mcg and vilanterol 25 mcg was also included as a treatment arm. Of the 609 subjects, 58% were female and 84% were Caucasian. The mean age was 40 years. The trial included a 4-week run-in period during which the subjects were symptomatic while taking their usual low- to mid-dose inhaled corticosteroid (fluticasone propionate 200 to 500 mcg/day or equivalent). If LABA were used prior to screening, their use was discontinued during the run-in. Mean baseline percent predicted FEV_1 was approximately 70% in both treatment groups. Twenty-six percent of subjects on placebo and 10% of subjects on ARNUITY ELLIPTA 100 mcg failed to complete the 12-week trial.

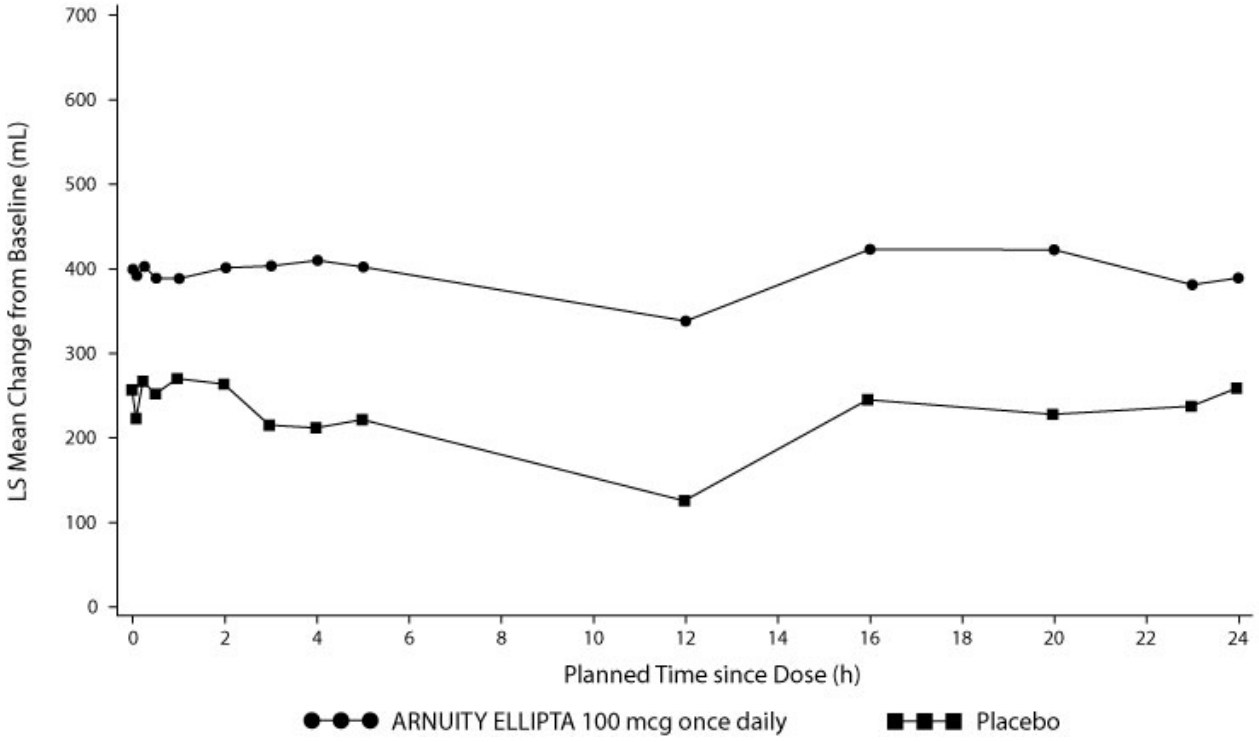
The co-primary efficacy endpoints in Trial 2 were change from baseline in trough FEV_1 at Week 12 and weighted mean FEV_1 (0-24 hours) at the end of the 12-week treatment period. Trough FEV_1 was assessed at clinic visits throughout the trial. Weighted mean FEV_1 (0-24 hours) was recorded at baseline and after the final study dose with serial measurements taken at

frequent intervals (at 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23, and 24 hours post-dose) in a subset of subjects (n = 201).

ARNUITY ELLIPTA 100 mcg once daily had greater mean changes from baseline in trough FEV_1 than placebo throughout the trial. At Week 12 or the last available on-treatment visit prior to Week 12, the mean change from baseline in trough FEV_1 was greater among subjects receiving ARNUITY ELLIPTA 100 mcg once daily than among those receiving placebo (mean treatment difference 136 mL; 95% CI: 51, 222).

Lung function improvements were sustained over the 24-hour period following the final dose of ARNUITY ELLIPTA 100 mcg (see Figure 4). Compared with placebo, at Week 12 the change from baseline in weighted mean FEV_1 was significantly greater for ARNUITY ELLIPTA 100 mcg (mean treatment difference 186 mL; 95% CI: 62, 310)

Figure 4. Mean Change from Baseline in Individual Serial FEV_1 (mL) Assessments after 12 Weeks of Treatment – Trial 2



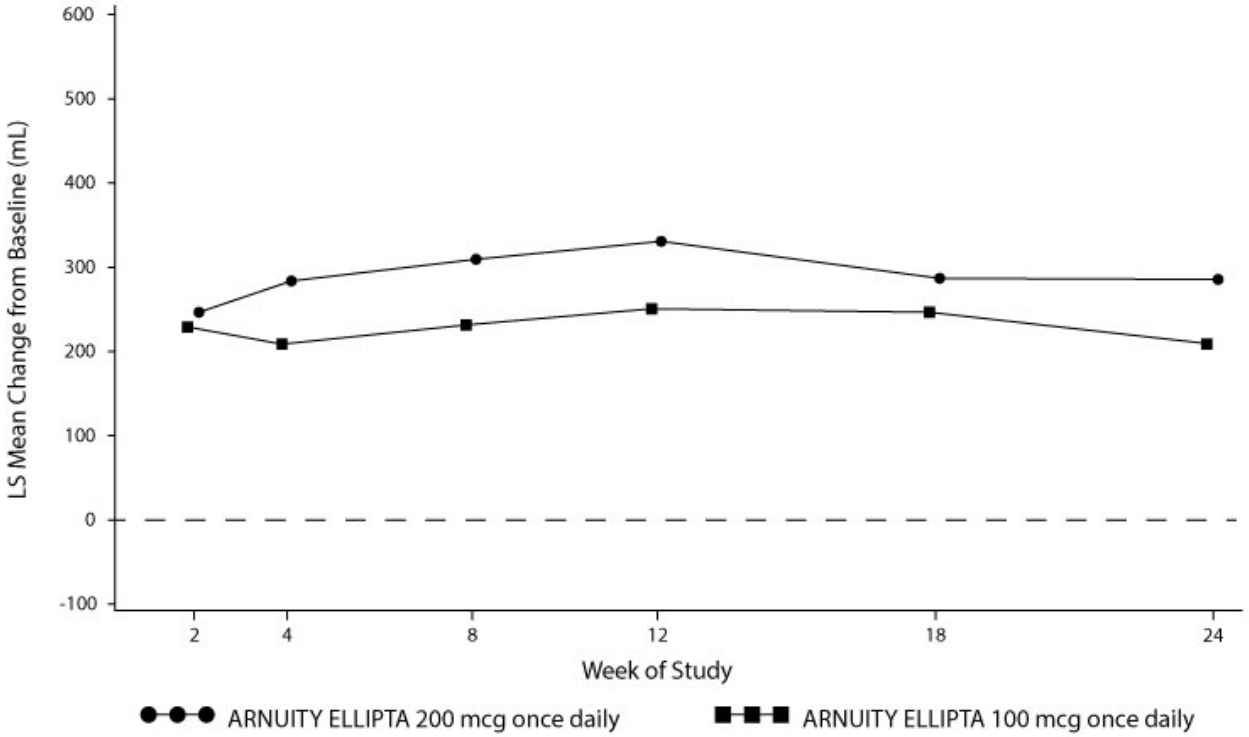
Subjects in both Trials 1 and 2 receiving ARNUITY ELLIPTA 100 mcg once daily had a greater improvement from baseline in percentage of 24-hour periods without need of $beta_2$-agonist rescue medication use than subjects receiving placebo.

Clinical Trial with ARNUITY ELLIPTA 200 mcg: Trial 3 was a 24-week trial that evaluated the relative efficacy of ARNUITY ELLIPTA 100 mcg and ARNUITY ELLIPTA 200 mcg on lung function in subjects with asthma. Of the 219 subjects, 68% were female and 87% were Caucasian. The mean age was 46 years. The trial included a 4-week run-in period during

which the subjects were symptomatic while taking their usual mid- to high-dose inhaled corticosteroid therapy (i.e., fluticasone propionate greater than 250 to 1,000 mcg/day or equivalent). If LABA were used prior to screening, their use was discontinued during the run-in. Mean baseline percent predicted FEV_1 was approximately 68% overall and similar in the 2 treatment groups. Sixteen percent of subjects on ARNUITY ELLIPTA 100 mcg and 13% of subjects on ARNUITY ELLIPTA 200 mcg failed to complete the 24-week trial.

The primary efficacy endpoint was mean change from baseline in trough FEV_1 at Week 24. There were trends toward greater mean changes from baseline in the group receiving ARNUITY ELLIPTA 200 mcg than the group receiving ARNUITY ELLIPTA 100 mcg throughout the trial (see Figure 5). At Week 24 or the last available on-treatment visit prior to Week 24, the mean change from baseline in trough FEV_1 was 208 mL for ARNUITY ELLIPTA 100 mcg, as compared to 284 mL for ARNUITY ELLIPTA 200 mcg (difference of 77 mL; 95% CI: -39, 192) as seen in Figure 3.

Figure 5. Mean Change from Baseline in Trough FEV_1 (mL) over Time – Trial 3



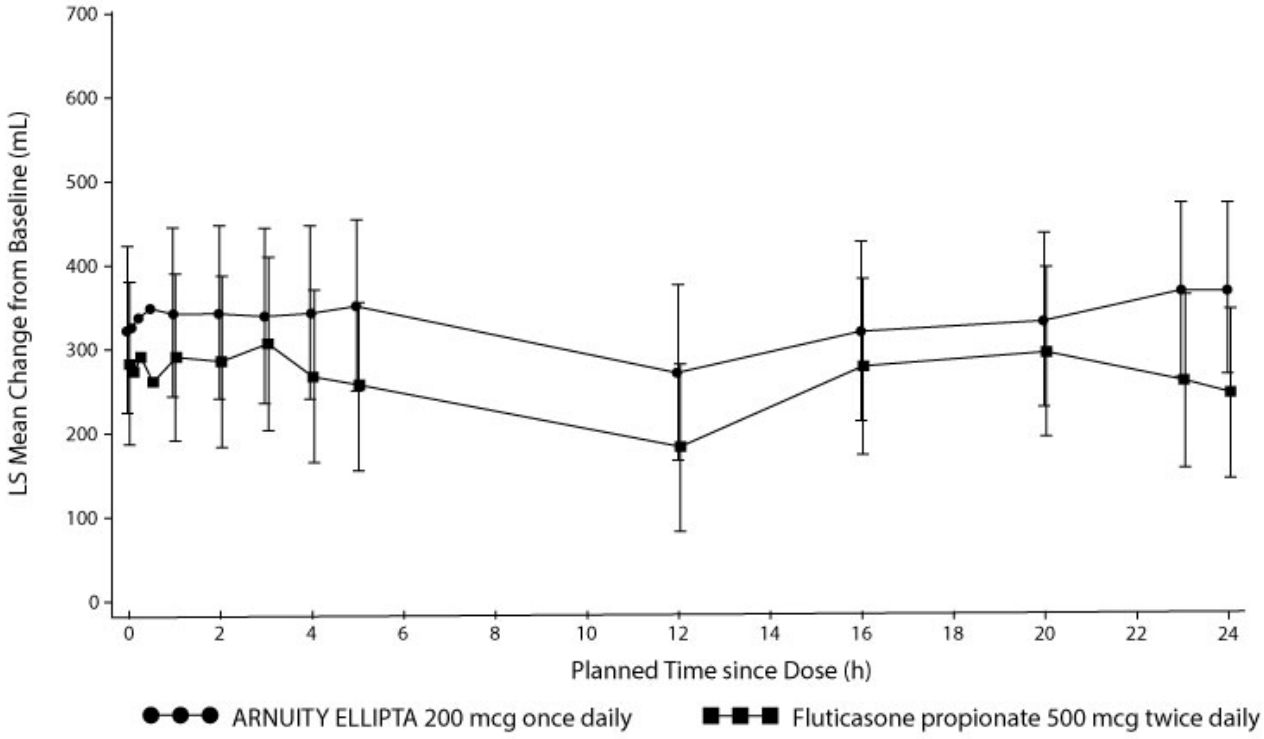
Trial 4 was a 24-week trial that evaluated the efficacy of ARNUITY ELLIPTA 200 mcg once daily and fluticasone propionate 500 mcg twice daily on lung function in subjects with asthma. The combination of fluticasone furoate 200 mcg and vilanterol 25 mcg was also included as a treatment arm (data not shown). Of the 586 subjects, 59% were female and 84% were Caucasian. The mean age was 46 years. The trial included a 4-week run-in period during which the subjects were symptomatic while taking their usual mid- to high-dose inhaled

corticosteroid (fluticasone propionate 500 to 1,000 mcg/day or equivalent). If LABA were used prior to screening, their use was discontinued during the run-in. Mean baseline percent predicted FEV_1 was approximately 67% in both treatment groups.

Both ARNUITY ELLIPTA 200 mcg once daily and fluticasone propionate 500 mcg twice daily produced improvement from baseline in lung function. At Week 24 the mean change from baseline in trough FEV_1 was 201 mL for ARNUITY ELLIPTA 200 mcg once daily and 183 mL for fluticasone propionate 500 mcg twice daily (treatment difference of 18 mL, 95% CI: -66, 102).

Lung function improvements were sustained over the 24-hour period following the final dose of ARNUITY ELLIPTA 200 mcg (see Figure 6). At Week 24, the change from baseline in weighted mean FEV_1 was 328 mL for ARNUITY ELLIPTA 200 mcg once daily and 258 mL for fluticasone propionate 500 twice daily (difference of 70 mL; 95% CI: -67, 208).

Figure 6. Mean Change from Baseline in Individual Serial FEV_1 (mL) Assessments after 24 Weeks of Treatment – Trial 4



16 HOW SUPPLIED/STORAGE AND HANDLING

ARNUITY ELLIPTA 100 is supplied as a disposable light grey and orange plastic inhaler containing a foil strip with 30 blisters (NDC 0173-0874-10) or 14 blisters (institutional pack) (NDC 0173-0874-14).

ARNUITY ELLIPTA 200 is supplied as a disposable light grey and orange plastic inhaler containing a foil strip with 30 blisters (NDC 0173-0876-10) or 14 blisters (institutional pack) (NDC 0173-0876-14).

The inhaler is packaged in a moisture-protective foil tray with a desiccant and a peelable lid.

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. Keep out of reach of children.

ARNUITY ELLIPTA should be stored inside the unopened moisture-protective foil tray and only removed from the tray immediately before initial use. Discard ARNUITY ELLIPTA 6 weeks after opening the foil tray or when the counter reads "0" (after all blisters have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Not for Acute Symptoms: Inform patients that ARNUITY ELLIPTA is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. ARNUITY ELLIPTA is not a bronchodilator and should not be used to treat status asthmaticus or to relieve acute asthma symptoms. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Symptoms get worse
- Significant decrease in lung function as outlined by the physician
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists

Advise patients not to increase the dose or frequency of ARNUITY ELLIPTA. The daily dosage of ARNUITY ELLIPTA should not exceed 1 inhalation. If they miss a dose, instruct patients to take their next dose at the same time they normally do.

Tell patients they should not stop or reduce therapy with ARNUITY ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

Local Effects: Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat it with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with ARNUITY ELLIPTA therapy, but at times therapy with ARNUITY ELLIPTA may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.

Immunosuppression: Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their

physicians without delay. Inform patients of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections or ocular herpes simplex.

Hypercorticism and Adrenal Suppression: Advise patients that ARNUITY ELLIPTA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, instruct that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to ARNUITY ELLIPTA.

Reduction in Bone Mineral Density: Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity: Inform patients that orally inhaled corticosteroids, including ARNUITY ELLIPTA, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route.

Ocular Effects: Advise patients that long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

Hypersensitivity Reactions Including Anaphylaxis: Advise patients that hypersensitivity reactions (e.g., urticaria, flushing, allergic dermatitis, bronchospasm), including anaphylaxis, may occur after administration of ARNUITY ELLIPTA. Instruct patients to 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 medications containing lactose; therefore, patients with severe milk protein allergy should not use ARNUITY ELLIPTA.

Use Daily for Best Effect: Advise patients to use ARNUITY ELLIPTA at regular intervals, since its effectiveness depends on regular use. Maximum benefit may not be achieved for 1 week or longer after starting treatment. If symptoms do not improve after 2 weeks of therapy or if the condition worsens, instruct patients to contact their physicians.

ARNUITY is a trademark and ELLIPTA is a registered trademark of the GSK group of companies.

GlaxoSmithKline
Research Triangle Park, NC 27709

XXX:xPI

Patient Information

ARNUITY™ ELLIPTA® *[ar-NEW-i-tee ee-LIP-ta]* (fluticasone furoate inhalation powder) 100 mcg

ARNUITY™ ELLIPTA® (fluticasone furoate inhalation powder) 200 mcg

Read the Patient Information that comes with ARNUITY ELLIPTA before you start using it and each time you get a refill. There may be new information. This Patient Information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is ARNUITY ELLIPTA?

ARNUITY ELLIPTA is an inhaled corticosteroid (ICS) medicine used for the control and prevention of asthma in adults and children aged 12 years and older.

- ARNUITY ELLIPTA helps to prevent and control symptoms of asthma.
- **ARNUITY ELLIPTA is not for use to treat sudden symptoms of an asthma attack, wheezing, cough, shortness of breath, and chest pain or tightness.** Always have a rescue inhaler (an inhaled, short-acting bronchodilator) with you to treat sudden symptoms. If you do not have a rescue inhaler, contact your healthcare provider to have one prescribed for you.
- It is not known if ARNUITY ELLIPTA is safe and effective in children younger than 12 years.

Who should not use ARNUITY ELLIPTA?

Do not use ARNUITY ELLIPTA:

- to treat sudden symptoms of asthma. **ARNUITY ELLIPTA is not a rescue inhaler and should not be used to give you fast relief from your asthma attack.** Always use a rescue inhaler, such as albuterol, during a sudden asthma attack.
- if you have a severe allergy to milk proteins. Ask your healthcare provider if you are not sure.
- are allergic to fluticasone furoate or any of the ingredients in ARNUITY ELLIPTA. See “What are the ingredients in ARNUITY ELLIPTA?” below for a complete list of ingredients.

What should I tell my healthcare provider before using ARNUITY ELLIPTA?

Tell your healthcare provider about all of your health conditions, including if you:

- have liver problems.
- have weak bones (osteoporosis).
- have an immune system problem.
- have eye problems such as glaucoma or cataracts.
- are allergic to any of the ingredients in ARNUITY ELLIPTA, any other medicines, or food products. See "What are the ingredients in ARNUITY ELLIPTA?" below for a complete list of ingredients.
- have any type of viral, bacterial, or fungal infection.
- are exposed to chickenpox or measles.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if ARNUITY ELLIPTA may harm your unborn baby.
- are breastfeeding. It is not known if the medicine in ARNUITY ELLIPTA passes into your milk and if it can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ARNUITY ELLIPTA and certain other medicines may interact with each other. This may cause serious side effects. Especially, tell your healthcare provider if you take antifungal, anti-HIV, or any other corticosteroid medicines. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use ARNUITY ELLIPTA?

Read the step-by-step instructions for using ARNUITY ELLIPTA at the end of this Patient Information.

- **Do not** use ARNUITY ELLIPTA unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- ARNUITY ELLIPTA comes in 2 different strengths. Your healthcare provider prescribed the strength that is best for you.
- Use ARNUITY ELLIPTA exactly as your healthcare provider tells you to use it. **Do not** use ARNUITY ELLIPTA more often than prescribed.
- Adolescents may need help to use ARNUITY ELLIPTA.

- Use 1 inhalation of ARNUITY ELLIPTA 1 time each day. Use ARNUITY ELLIPTA at the same time each day.
- If you miss a dose of ARNUITY ELLIPTA, take it as soon as you remember. Do not take more than 1 inhalation each day. Take your next dose at your usual time. Do not take 2 doses at one time.
- Do not stop using ARNUITY ELLIPTA unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **ARNUITY ELLIPTA does not relieve sudden symptoms.** Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:
  - your breathing problems get worse
  - you need to use your rescue inhaler more often than usual
  - your rescue inhaler does not work as well to relieve your symptoms
  - you need to use 4 or more inhalations of your rescue inhaler in 24 hours for 2 or more days in a row
  - you use 1 whole canister of your rescue inhaler in 8 weeks
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.

What are the possible side effects with ARNUITY ELLIPTA?

ARNUITY ELLIPTA can cause serious side effects, including:

- **fungal infection in your mouth or throat (thrush).** Rinse your mouth with water without swallowing after using ARNUITY ELLIPTA to help reduce your chance of getting thrush
- **weakened immune system and increased chance of getting infections (immunosuppression)**
- **reduced adrenal function (adrenal insufficiency).** Adrenal insufficiency is a condition where the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines (such as prednisone) and start taking a medicine containing an inhaled corticosteroid (such as ARNUITY ELLIPTA). When your body is under stress from fever, trauma (such as a car accident), infection, surgery, or worse asthma symptoms, adrenal insufficiency can get worse and may cause death.

  Symptoms of adrenal insufficiency include:
  - feeling tired

- lack of energy
- weakness
- nausea and vomiting
- low blood pressure

- **sudden breathing problems immediately after inhaling your medicine**
- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of your face, mouth, and tongue
  - breathing problems
- **bone thinning or weakness (osteoporosis)**
- **slow growth in adolescents.** An adolescent's growth should be checked often.
- **eye problems including glaucoma and cataracts.** You should have regular eye exams while using ARNUITY ELLIPTA.

Common side effects of ARNUITY ELLIPTA include:

- runny nose and sore throat
- headache
- breathing problems (bronchitis)
- flu

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with ARNUITY ELLIPTA. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store ARNUITY ELLIPTA?

- Store ARNUITY ELLIPTA at room temperature between 68°F and 77°F (20°C and 25°C). Keep in a dry place away from heat and sunlight.
- Store ARNUITY ELLIPTA in the unopened foil tray and only open when ready for use.
- Safely throw away ARNUITY ELLIPTA in the trash 6 weeks after you open the foil tray or when the counter reads "0", whichever comes first. Write the date you open the tray on the label on the inhaler.

- **Keep ARNUITY ELLIPTA and all medicines out of the reach of children.**

General information about ARNUITY ELLIPTA

Medicines are sometimes prescribed for purposes not mentioned in a Patient Information leaflet. Do not use ARNUITY ELLIPTA for a condition for which it was not prescribed. Do not give your ARNUITY ELLIPTA to other people, even if they have the same condition that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about ARNUITY ELLIPTA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ARNUITY ELLIPTA that was written for healthcare professionals.

For more information about ARNUITY ELLIPTA, call 1-888-825-5249 or visit our website at www.ARNUITY.com.

What are the ingredients in ARNUITY ELLIPTA?

Active ingredients: fluticasone furoate
Inactive ingredients: lactose monohydrate (contains milk proteins)

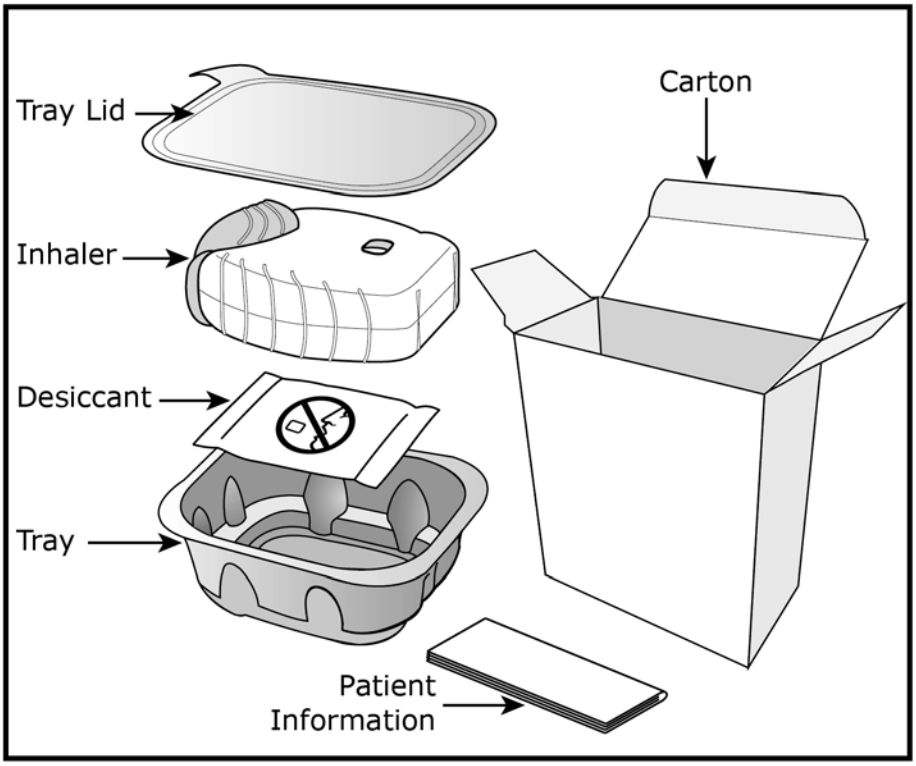
Instructions for Use

For Oral Inhalation Only.

Read this before you start:

- **If you open and close the cover without inhaling the medicine, you will lose the dose.**
- **The lost dose will be securely held inside the inhaler, but it will no longer be available to be inhaled.**
- **It is not possible to accidentally take a double dose or an extra dose in 1 inhalation.**

Your ARNUITY ELLIPTA inhaler



How to use your inhaler

- ARNUITY ELLIPTA comes in a foil tray.
- Peel back the lid to open the tray. See Figure A.
- The tray contains a desiccant to reduce moisture. Do not eat or inhale. Throw it away in the household trash out of reach of children and pets. See Figure B.

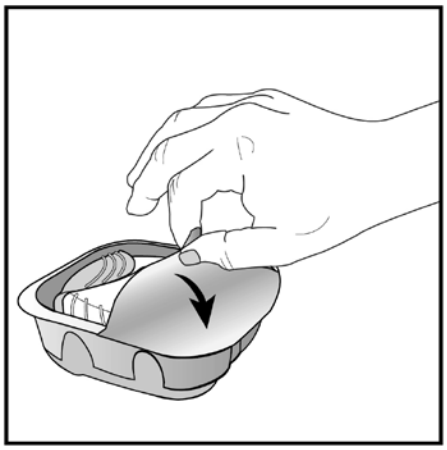


Figure A

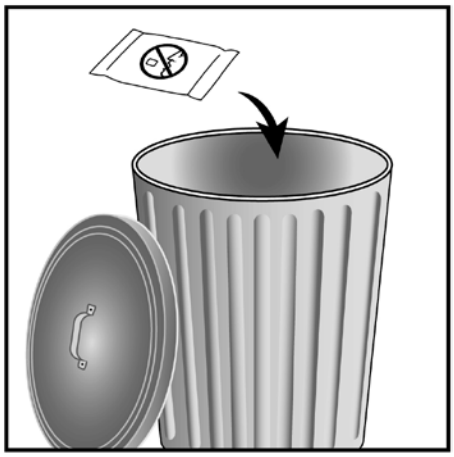


Figure B

Important Notes:

- Your inhaler contains 30 doses (14 doses if you have a sample or institutional pack).
- Each time you fully open the cover of the inhaler (you will hear a clicking sound), a dose is ready to be inhaled. This is shown by a decrease in the number on the counter.
- If you open and close the cover without inhaling the medicine, you will lose the dose. The lost dose will be held in the inhaler, but it will no longer be available to be inhaled. It is not possible to accidentally take a double dose or an extra dose in 1 inhalation.
- **Do not** open the cover of the inhaler until you are ready to use it. To avoid wasting doses after the inhaler is ready, **do not** close the cover until after you have inhaled the medicine.
- Write the "Tray opened" and "Discard" dates on the inhaler label. The "Discard" date is 6 weeks from the date you open the tray.

Check the counter. See Figure C.

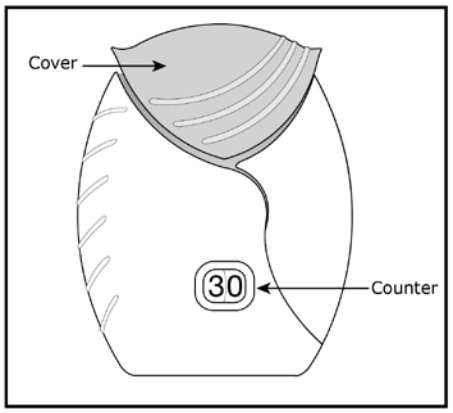


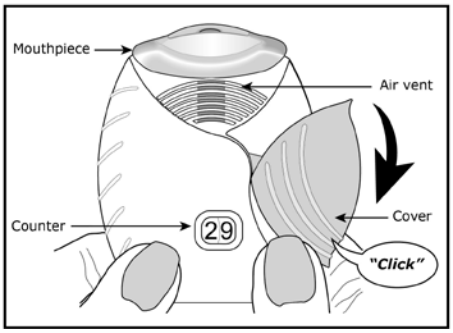
Figure C

- Before the inhaler is used for the first time, the counter should show the number 30 (14 if you have a sample or institutional pack). This is the number of doses in the inhaler.
- Each time you open the cover, you prepare 1 dose of medicine.
- The counter counts down by 1 each time you open the cover.

Prepare your dose:

Wait to open the cover until you are ready to take your dose.

Figure D



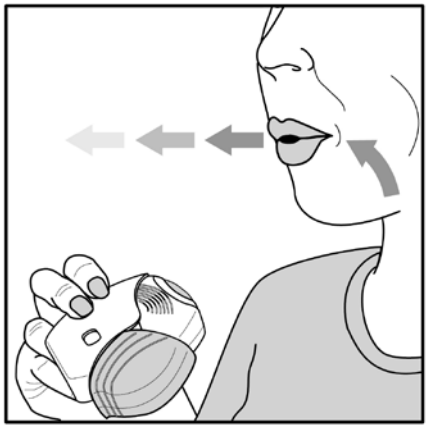


Figure E

Step 1. Open the cover of the inhaler. See Figure D.

- Slide the cover down to expose the mouthpiece. You should hear a “click.” The counter will count down by 1 number. You do not need to shake this kind of inhaler. **Your inhaler is now ready to use.**
- If the counter does not count down as you hear the click, the inhaler will not deliver the medicine. Call your healthcare provider or pharmacist if this happens.

Step 2. Breathe out. See Figure E.

- While holding the inhaler away from your mouth, breathe out (exhale) fully. Do not breathe out into the mouthpiece.

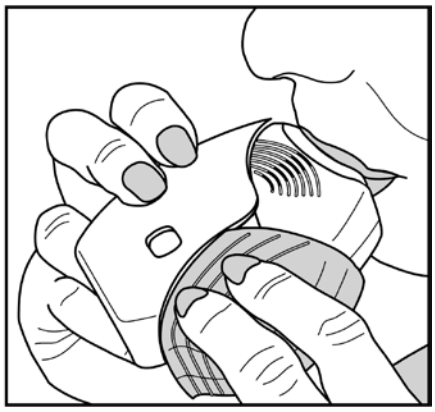


Figure F

Step 3. Inhale your medicine. See Figure F.

- Put the mouthpiece between your lips, and close your lips firmly around it. Your lips should fit over the curved shape of the mouthpiece.
- Take 1 long, steady, deep breath in through your mouth. **Do not** breathe in through your nose.

Figure G

- Do not block the air vent with your fingers. **See Figure G.**

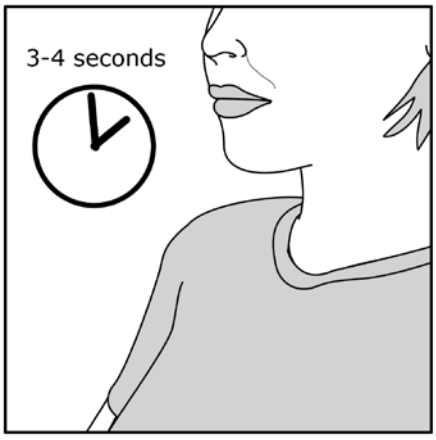


Figure H

- **Remove the inhaler from your mouth and hold your breath for about 3 to 4 seconds** (or as long as comfortable for you). **See Figure H.**

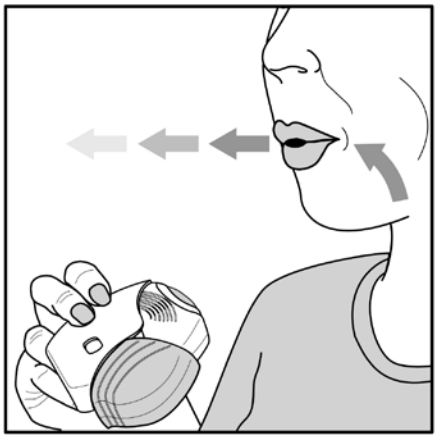


Figure I

Step 4. Breathe out slowly and gently. See Figure I.

- You may not taste or feel the medicine, even when you are using the inhaler correctly.
- **Do not** take another dose from the inhaler even if you do not feel or taste the medicine.

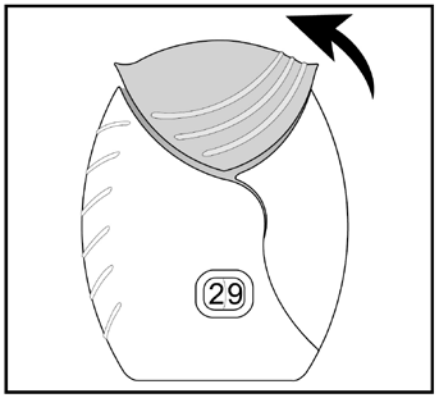


Figure J

Step 5. Close the inhaler. See Figure J.

- You can clean the mouthpiece if needed, using a dry tissue, before you close the cover. Routine cleaning is not required.
- Slide the cover up and over the mouthpiece as far as it will go.

Figure K

Step 6. Rinse your mouth. See Figure K.

- Rinse your mouth with water after you have used the inhaler and spit the water out. **Do not** swallow the water.

Important Note: When should you get a refill?

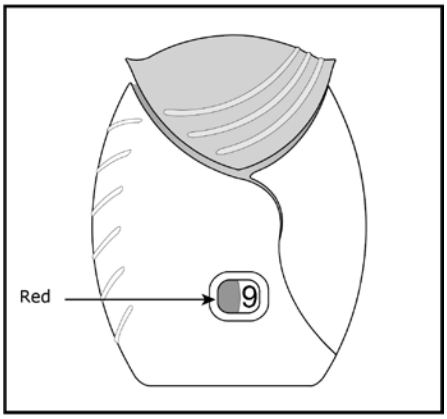


Figure L

- **When you have less than 10 doses remaining** in your inhaler, the left half of the counter shows red as a reminder to get a refill. **See Figure L.**
- After you have inhaled the last dose, the counter will show "0" and will be empty.
- Throw the empty inhaler away in your household trash out of reach of children and pets.

If you have questions about ARNUITY ELLIPTA or how to use your inhaler, call GlaxoSmithKline (GSK) at 1-888-825-5249 or visit www. ARNUITY.com.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

GlaxoSmithKline
Research Triangle Park, NC 27709

August 2014
XXX:xPIL