

PRODUCT MONOGRAPH

Pr **ARNUITY ELLIPTA**

fluticasone furoate dry powder for oral inhalation

100 mcg and 200 mcg

Inhaled corticosteroid

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Pr **ARNUITY ELLIPTA**

fluticasone furoate dry powder for oral inhalation

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral Inhalation	Dry powder for oral inhalation/ 100 mcg fluticasone furoate 200 mcg fluticasone furoate	Lactose monohydrate (which contains milk protein)

INDICATIONS AND CLINICAL USE

ARNUITY ELLIPTA (fluticasone furoate) is indicated for the once-daily maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years and older.

ARNUITY ELLIPTA is **not** indicated for the relief of acute bronchospasm (see WARNINGS AND PRECAUTIONS, General).

Geriatrics (≥ 65 years of age):

No dosage adjustment is required in patients over 65 years of age.

Pediatrics (< 12 years of age):

The safety and efficacy of ARNUITY ELLIPTA have not been established in children less than 12 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to fluticasone furoate or to any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Patients with severe hypersensitivity to milk proteins (see WARNINGS AND PRECAUTIONS, Hypersensitivity).
- In the primary treatment of status asthmaticus or other acute episodes of asthma.

WARNINGS AND PRECAUTIONS

General

Acute Asthma Episodes

ARNUIITY ELLIPTA is not a bronchodilator and is not indicated for rapid relief of bronchospasm. An inhaled, short-acting beta₂-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 beta₂-agonist for treatment of acute symptoms, despite regular once-daily use of ARNUITY ELLIPTA. Patients should be instructed to contact their physician immediately if episodes of asthma not responsive to their usual doses of bronchodilators occur during the course of treatment with ARNUITY ELLIPTA. During such episodes, patients may require therapy with oral corticosteroids.

Carcinogenesis and Mutagenesis

Animal data only (see TOXICOLOGY).

Ear/Nose/Throat

Oropharyngeal Candidiasis

Localized infections of the mouth and pharynx with *Candida albicans*, which are associated with the use of inhaled glucocorticosteroids, have occurred in patients treated with ARNUITY ELLIPTA during clinical studies. Patients should therefore be advised to rinse their mouth with water (without swallowing) after inhalation of ARNUITY ELLIPTA to reduce the risk of oropharyngeal candidiasis.

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. However, at times, therapy with ARNUITY ELLIPTA may need to be interrupted for the treatment of severe infections (see DRUG INTERACTIONS, Drug-Drug Interactions).

Endocrine and Metabolism

Systemic Effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur with inhaled corticosteroids than with oral corticosteroids. Possible systemic effects of ARNUITY ELLIPTA include: Cushing's syndrome, Cushingoid features, hypothalamic-pituitary-adrenal (HPA) axis suppression, decrease in bone mineral density (BMD), growth retardation in children and adolescents, cataracts and glaucoma.

Hypercorticism and Adrenal Suppression

Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic dose of ARNUITY ELLIPTA. However, exceeding the recommended dosage or co-administration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction (see DRUG INTERACTIONS, Drug-Drug Interactions).

It is possible that systemic corticosteroid effects, such as hypercorticism and adrenal suppression (including adrenal crisis), may appear in a small number of patients who are sensitive to these effects. In light of the possibility of 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. If such effects occur, ARNUITY ELLIPTA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and other treatments for management of asthma symptoms should be considered.

Systemic Steroid Replacement by Inhaled Steroid

Particular care is needed for patients who have been 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 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 control asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid 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 immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to ARNUITY ELLIPTA. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with ARNUITY ELLIPTA. Lung function (mean forced expiratory volume in 1 second [FEV₁] or morning peak expiratory flow [AM PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral 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.

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 consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, 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.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric and adolescent patients (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics). Monitor the growth of adolescent patients receiving ARNUITY ELLIPTA (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including ARNUITY ELLIPTA, titrate to the lowest dose that effectively controls symptoms.

Hypersensitivity

Immediate hypersensitivity reactions may occur after administration of ARNUITY ELLIPTA. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, ARNUITY ELLIPTA should be discontinued immediately and alternative therapy instituted. The patient should NOT be re-challenged with ARNUITY ELLIPTA if this is identified as the cause of the hypersensitivity reaction (see CONTRAINDICATIONS).

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).

Immune

Patients who are 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 patients using corticosteroids. In such patients who have not had these diseases or 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) 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.

As with all medications containing a corticosteroid, ARNUITY ELLIPTA should be administered with caution, and only if necessary, in patients with active or quiescent tuberculosis infections of the respiratory tract; chronic or untreated infections, such as systemic fungal, bacterial, viral, or parasitic; or ocular herpes simplex.

Ophthalmologic

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.

Respiratory

Paradoxical bronchospasm

As with other inhalation therapies, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a rapid onset, short-acting inhaled bronchodilator such as salbutamol. ARNUITY ELLIPTA should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Pneumonia

In studies in patients with asthma, no difference was observed in the incidence of pneumonia with ARNUITY ELLIPTA 100 mcg compared to placebo. An increased incidence of pneumonia in asthmatic patients with higher doses of inhaled corticosteroids cannot be excluded.

An increase in the incidence of pneumonia has been observed in patients with Chronic Obstructive Pulmonary Disease (COPD) receiving inhaled corticosteroids.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies 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 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.

Labour and Delivery: There are no adequate and well-controlled human studies that have investigated the effects of ARNUITY ELLIPTA during labour and delivery.

Nursing Women: It is not known whether fluticasone furoate is excreted in human breast milk. However, other corticosteroids have been detected in human milk. A risk to breastfed newborns/infants cannot be excluded. 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, the use of ARNUITY ELLIPTA by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

Pediatrics: The safety and efficacy of ARNUITY ELLIPTA have not been established in children less than 12 years of age.

Geriatrics: 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.

Hepatic Impairment: Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with mild, moderate and severe hepatic impairment compared with healthy subjects. Use ARNUITY ELLIPTA with caution in patients with hepatic impairment. For patients with moderate or severe hepatic impairment, the maximum dose is ARNUITY ELLIPTA 100 mcg (see DOSAGE AND ADMINISTRATION). Patients should be monitored for corticosteroid-related side effects.

Renal Impairment: There were no significant increases in fluticasone furoate exposure in subjects with severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests

Patients with hepatic impairment should be monitored for corticosteroid effects due to potentially increased systemic exposure of fluticasone furoate.

Physicians should monitor the growth of children and adolescents taking corticosteroids by any route.

For patients at risk, monitoring of bone and ocular effects (cataract and glaucoma) should also be considered in patients receiving maintenance therapy with ARNUITY ELLIPTA.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection
- Immunosuppression
- Hypercorticism and adrenal suppression
- Reduction in BMD
- Growth effects in pediatrics
- Glaucoma and cataracts

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The clinical program for fluticasone furoate in the ELLIPTA inhaler included 10 double-blind, parallel-group, controlled studies (7 with placebo) in 6,219 patients with asthma who ranged in age from 12 to 84 years. The studies ranged in duration from 8 to 76 weeks. Doses of fluticasone furoate studied ranged from 25 to 800 mcg. ARNUITY ELLIPTA 100 mcg was studied in 1,663 patients and ARNUITY ELLIPTA 200 mcg was studied in 608 patients. The majority of the patients who received ARNUITY ELLIPTA were female (66% of the group receiving the 100 mcg strength and 62% of the group receiving the 200 mcg strength).

The safety profile of fluticasone furoate was generally consistent with the known class effects of an ICS.

12-week and 24-week Studies

The incidence of adverse events associated with ARNUITY ELLIPTA in Table 1 is based on one 12-week (HZA106827) and three 24-week studies (FFA112059, FFA114496 and HZA106829) of ARNUITY ELLIPTA 100 mcg and ARNUITY ELLIPTA 200 mcg in 1,378 adolescent and adult patients with asthma. Two of the studies had a placebo arm (HZA106827 and FFA112059). Patients received one inhalation once-daily of ARNUITY ELLIPTA 100 mcg or 200 mcg. Other treatments included fluticasone propionate 250 mcg and 500 mcg twice daily. Subject withdrawals due to adverse events was low across all treatment groups (<1% to 2%). Adverse events observed in the other studies were consistent with those described below.

Adverse events in subjects receiving ARNUITY ELLIPTA reported with a frequency of equal to or greater than 1%, and exceeding the rate in subjects receiving placebo are listed in Table 1.

Table 1 Adverse Events With $\geq 1\%$ Incidence and More Common than Placebo with ARNUITY ELLIPTA in Subjects with Asthma

Adverse Event	ARNUIITY ELLIPTA 200 mcg (n=313) %	ARNUIITY ELLIPTA 100 mcg (n=438) %	Placebo (n= 318) %
Infections and Infestations			
Nasopharyngitis	13	8	7
Bronchitis	4	5	3
Upper respiratory tract infection	3	3	2
Sinusitis	4	3	<1
Pharyngitis	2	3	2
Influenza	5	1	0
Respiratory tract infection viral	3	<1	0
Oral candidiasis	2	1	0
Rhinitis	2	<1	0
Oropharyngeal candidiasis	<1	1	0
Gastroenteritis	<1	1	<1
Cystitis	1	<1	<1
Respiratory, Thoracic and Mediastinal Disorders			
Oropharyngeal pain	4	2	<1
Cough	3	<1	1
Dysphonia	2	1	0
Rhinitis allergic	<1	1	<1
Nasal congestion	<1	1	<1
Respiratory disorder	1	0	0
Nervous System Disorders			
Headache	9	6	4
Gastrointestinal Disorders			
Toothache	1	2	<1
Abdominal pain	2	0	<1
Abdominal pain upper	<1	1	<1
Diarrhea	1	<1	<1
Injury, Poisoning and Procedural Complications			
Procedural pain	1	<1	<1
Musculoskeletal and Connective Tissue Disorders			
Back pain	3	3	<1
Vascular Disorders			
Hypertension	1	<1	0

Studies FFA112059, FFA114496, HZA106827 and HZA106829

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse events were seen at a frequency of <1%.

Infections and Infestations: oral herpes, respiratory tract infection, vaginal infection, viral infection, abscess, herpes zoster, otitis externa, tooth abscess, tooth infection, viral pharyngitis, vulvovaginal mycotic infection, bacterial rhinitis, *Escherichia* bacteraemia, folliculitis, gastrointestinal viral infection, gingivitis, *haemophilus* infection, infection, laryngitis viral, localised infection, lower respiratory tract infection, nail infection, otitis media, pharyngotonsillitis, pulpitis dental, skin infection, tonsillitis bacterial, viral rhinitis, viral tracheitis, viral upper respiratory tract infection.

Respiratory, Thoracic and Mediastinal Disorders: rhinitis seasonal, respiratory tract congestion, epistaxis, interstitial lung disease, snoring, vocal cord inflammation, asthma exercise induced.

Nervous System Disorders: intercostal neuralgia, syncope, migraine, tremor, presyncope, sciatica, somnolence.

Gastrointestinal Disorders: gastritis, dry mouth, cheilitis, constipation, Crohn's disease, diverticulum, irritable bowel syndrome, odynophagia, oral mucosa erosion, pancreatitis.

Musculoskeletal and Connective Tissue Disorders: arthralgia, chest pain, osteoarthritis, chondromalacia, chondropathy, fibromyalgia, intervertebral disc degeneration, intervertebral disc protrusion, osteitis, osteochondrosis, osteoporosis, spondylolisthesis.

Injury, Poisoning and Procedural Complications: ligament sprain, hand fracture, rib fracture, animal bite, forearm fracture, joint dislocation, laceration, meniscus lesion, nail injury, post-traumatic neck syndrome.

Skin and Subcutaneous Tissue Disorders: acne, blister, rash generalised.

General Disorders and Administration Site Conditions: influenza like illness, asthenia, chills, facial pain, edema peripheral.

Skin and Subcutaneous Tissue Disorders: dermatitis allergic, dermatitis atopic, dermatitis.

Vascular Disorders: thrombophlebitis, hypertensive crisis, venous thrombosis.

Cardiac Disorders: palpitations, angina pectoris, congestive cardiomyopathy, ventricular extrasystoles.

Investigations: body temperature increased, blood glucose increased, blood pressure increased, hepatic enzyme increased.

Psychiatric Disorders: insomnia, sleep disorder, anxiety disorder, depression.

Reproductive System and Breast Disorders: breast pain, epididymal cyst, metrorrhagia.

Immune System Disorders: seasonal allergy, food allergy, iodine allergy.

Eye Disorders: eyelid edema, cataract, conjunctivitis, conjunctivitis allergic, eye pruritus.

Metabolism and Nutrition Disorders: diabetes mellitus, hypercholesterolemia.

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps): oral papilloma, prostate cancer, thymoma.

Hepatobiliary disorders: cholecystitis acute.

Renal and Urinary Disorders: cystitis haemorrhagic, renal colic.

Endocrine Disorders: hypothyroidism.

Ear and Labyrinth Disorders: eustachian tube obstruction.

Social Circumstances: stress at work.

Post-Market Adverse Drug Reactions

There are currently no post-marketing data available for ARNUITY ELLIPTA 100 mcg or 200 mcg.

The following relevant adverse reactions have been identified from post-approval use of fluticasone furoate intranasal spray for allergic rhinitis:

- Reports of headache have been common. Rare reports of hypersensitivity reactions, including anaphylaxis, angioedema, dyspnoea, rash and urticaria.

Because these reactions are reported voluntarily from intranasal use of fluticasone furoate in an allergic rhinitis population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure relative to use of an inhaled formulation of fluticasone furoate in an asthma population.

DRUG INTERACTIONS

Drug-Drug Interactions

Inhibitors of Cytochrome P450 3A4

Fluticasone furoate is rapidly cleared by extensive first pass metabolism mediated by the liver enzyme CYP3A4.

Inhibitors of P-glycoprotein (P-gp)

Fluticasone furoate is a substrate for P-gp, however, concomitant administration of fluticasone furoate with P-gp inhibitors is considered unlikely to alter fluticasone furoate systemic exposure. Clinical pharmacology studies with selective P-gp inhibitors and fluticasone furoate have not been conducted.

Table 2 Established or Potential Drug-Drug Interactions

Drug Class	Ref	Effect	Clinical comment
Inhibitors of Cytochrome P450 3A4	CT	May increase the systemic exposure to fluticasone furoate, which could lead to an increase in potential for adverse reactions.	Caution should be exercised when considering the co-administration 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).
Inhibitors of P-glycoprotein (P-gp)	T	Unlikely to alter fluticasone furoate systemic exposure	Clinical pharmacology studies with selective P-gp inhibitors and fluticasone furoate have not been conducted.

Abbreviations: CT = Clinical Trial, T = Theoretical

Drug-Food Interactions

Interactions with food have not been established. No clinically relevant effect of food would be expected and therefore a food interaction study was not conducted.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients should be made aware that for optimum benefit, ARNUITY ELLIPTA must be used regularly, even when asymptomatic.
- Patients should be regularly reassessed by a healthcare professional so that the dose of ARNUITY ELLIPTA they are receiving remains optimal and is only changed on medical advice.
- After asthma stability has been achieved, it is desirable to titrate to the lowest effective dosage to help reduce the possibility of side effects.

- 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.

Recommended Dose and Dosage Adjustment

The recommended dose is one inhalation of ARNUITY ELLIPTA 100 mcg or 200 mcg once-daily.

The starting dose is based on the patient's 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 adequately to one inhalation of ARNUITY ELLIPTA 100 mcg once-daily, switching to one inhalation of ARNUITY ELLIPTA 200 mcg once-daily may provide additional asthma control.

The highest recommended dose is one inhalation of ARNUITY ELLIPTA 200 mcg once-daily. The safety and efficacy of ARNUITY ELLIPTA when administered in excess of the recommended dose have not been established.

For break-through symptoms, an inhaled, short-acting beta₂-agonist (rescue medicine, e.g., salbutamol) should be taken as prescribed by a physician for immediate relief.

Dosing in Special Populations

Geriatrics (≥ 65 years of age)

No dosage adjustment is required in patients over 65 years of age (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Pediatrics (< 12 years of age)

The safety and efficacy of ARNUITY ELLIPTA have not been established in children less than 12 years of age. ARNUITY ELLIPTA is not recommended in children less than 12 years of age.

Hepatic Impairment

A clinical pharmacology study in subjects with mild, moderate and severe hepatic impairment showed up to 3-fold increase in systemic exposure to fluticasone furoate (both C_{max} and AUC) (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Impairment). Caution should be exercised when dosing patients with hepatic impairment as patients with hepatic impairment may be more at risk of systemic adverse reactions associated with corticosteroids.

For patients with moderate or severe hepatic impairment, the maximum dose is ARNUITY ELLIPTA 100 mcg.

Renal Impairment

No dose adjustment is required for patients with renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment).

Missed Dose

If a dose is missed, the patient should be instructed to take the next dose when it is due. The patient should be instructed not to take an extra dose.

Administration

ARNUITY ELLIPTA is for oral inhalation only.

ARNUITY ELLIPTA should be administered once-daily at the same time every day. Do not use ARNUITY ELLIPTA more than once every 24 hours. After inhalation, the patient should rinse their mouth with water (without swallowing) to help reduce the risk of oropharyngeal candidiasis.

OVERDOSAGE

An overdose of ARNUITY ELLIPTA may produce signs and symptoms consistent with the known inhaled corticosteroid class effects (see WARNINGS and PRECAUTIONS). Chronic overdosage (use at excessive doses for prolonged periods) may result in signs/symptoms of hypercorticism (see WARNINGS and PRECAUTIONS, Endocrine and Metabolism).

There is no specific treatment for an overdose with ARNUITY ELLIPTA. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the regional Poison Control Centre, where available.

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.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. Inflammation is an important component in the pathogenesis of asthma. The precise

mechanism through which fluticasone furoate affects asthma symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, basophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. Specific effects of fluticasone furoate demonstrated in *in vitro* and *in vivo* models included activation of the glucocorticoid response element, inhibition of pro-inflammatory transcription factors, such as NFκB resulting in inhibition of pro-inflammatory cytokines, and inhibition of antigen-induced lung eosinophilia in sensitized rats. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

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. *In vitro* studies have shown that translocation of the glucocorticoid receptor into the cell nucleus (essential for anti-inflammatory activity) is both more rapid and more prolonged with fluticasone furoate compared with fluticasone propionate. Nuclear localization of the glucocorticoid receptor was observed at 30 hours post-exposure with fluticasone furoate but not with fluticasone propionate. The clinical relevance of these findings is unknown.

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.

Pharmacodynamics

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

HPA Axis Effects:

Effects on HPA-axis function are known to occur with systemic administration of corticosteroids and this systemic side effect has also been reported with inhaled and intranasal corticosteroid use. Based on both clinical pharmacology and clinical data, inhaled fluticasone furoate at repeat doses up to 400 mcg was not consistently associated with statistically significant decreases in serum or urinary cortisol in healthy subjects. At higher doses, above the therapeutic range, corticosteroid class-related decreases in serum and urine cortisol levels were observed. In line with the increased fluticasone furoate systemic exposure, serum cortisol was reduced by approximately a third in subjects with moderate hepatic impairment after fluticasone furoate/vilanterol 200/25 mcg administration and a similar effect would be anticipated in subjects with severe hepatic impairment at this dose.

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).

Pharmacokinetics

Table 3 Summary of Fluticasone Furoate Pharmacokinetic Parameters in Healthy Subjects

ARNUIITY ELLIPTA	C _{max} (pg/mL) Geometric Mean (CV%)	AUC ₍₀₋₂₄₎ (pg.h/mL) Geometric Mean (CV%)	T _{max} (h) Median (range)
Fluticasone Furoate 100 mcg	28.8 (42.3)	373 (39.4)	0.50 (0.25, 3.00)
Fluticasone Furoate 200 mcg	49.0 (37.6)	643 (30.4)	0.75 (0.25, 3.00)

Table 4 Summary of Fluticasone Furoate (C_{max} and AUC₍₀₋₂₄₎) in Subjects with Asthma (Geometric Mean [95% CI])

ARNUIITY ELLIPTA	C _{max} (pg/mL)	AUC ₍₀₋₂₄₎ (pg.h/mL)
Fluticasone Furoate 100 mcg	27.0 [15.4, 50.3]	180.7 [117.4, 292.0]
Fluticasone Furoate 200 mcg	55.1 [32.6, 98.2]	394.5 [194.4, 917.8]

Absorption: Fluticasone furoate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. The absolute bioavailability for fluticasone furoate when administered by inhalation was, on average, 14%. The oral bioavailability of fluticasone furoate was low, on average, 1.3%. Given this low oral bioavailability, systemic exposure for fluticasone furoate following inhaled administration is primarily due to absorption of the inhaled portion of the dose delivered to the lung.

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

Metabolism: Following intravenous administration to healthy subjects, fluticasone furoate was cleared from systemic circulation principally by hepatic metabolism via CYP3A4 (total plasma clearance of 65.4 L/hr). Fluticasone furoate undergoes fast first pass metabolism and is primarily metabolized through hydrolysis of the S-fluoromethyl carbothioate group 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 dose, 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 and Conditions

Pediatrics: In adolescents (12 to 17 years of age), there are no recommended dose modifications. The safety and efficacy of ARNUITY ELLIPTA have not been established in children less than 12 years of age.

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. A reduction of growth velocity in children or teenagers 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 pediatric subjects. 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 pediatric subjects 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 (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 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 subjects were 474 pre-pubescent 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 patients 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 to 0.48) (see WARNINGS and PRECAUTIONS, Endocrine and Metabolism).

Geriatrics: There was no evidence for age (up to 84 years) to affect the pharmacokinetics of ARNUITY ELLIPTA in subjects with asthma.

Clinical trials of ARNUITY ELLIPTA for asthma included 285 subjects aged 65 and older (216 were treated with ARNUITY ELLIPTA 100 mcg or 200 mcg) and 32 subjects aged 75 and older (22 were treated with ARNUITY ELLIPTA 100 mcg or 200 mcg). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

Gender: A population pharmacokinetic analysis showed that no dose adjustment is required for fluticasone furoate based on the effect of gender.

Race: In subjects with asthma, estimates of fluticasone furoate $AUC_{(0-24)}$ for East Asian, Japanese and South East Asian subjects were up to 43% higher, on average, compared with Caucasian subjects. However, there was no evidence for the higher systemic exposure in these populations to be associated with a greater effect on adverse events such as HPA-axis suppression.

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, there was an increase in fluticasone furoate systemic exposure (up to three-fold as measured by $AUC_{(0-24)}$) in subjects with hepatic impairment compared with healthy subjects (Child-Pugh A, B or C). The increase in fluticasone furoate systemic exposure in subjects with moderate hepatic impairment (fluticasone furoate/vilanterol 200/25 mcg) was associated with an average 34% reduction in serum cortisol compared with healthy subjects (Child-Pugh B). Dose-normalized fluticasone furoate systemic exposure was similar in subjects with moderate and severe hepatic impairment (Child-Pugh B or C). For patients with moderate or severe hepatic impairment the maximum dose is 100 mcg.

Renal Impairment: A clinical pharmacology study of fluticasone furoate/vilanterol showed that severe renal impairment (creatinine clearance <30 mL/min) did not result in significantly greater exposure to fluticasone furoate or more marked corticosteroid systemic effects compared with healthy subjects. No dose adjustment is required for patients with renal impairment. The effects of hemodialysis have not been studied.

STORAGE AND STABILITY

Do not store above 25°C. Store in a dry place away from direct heat or sunlight. If stored in a refrigerator, the inhaler should be allowed to return to room temperature for at least one hour before use.

Keep out of sight and reach of children.

SPECIAL HANDLING INSTRUCTIONS

ARNUITY ELLIPTA is provided in a foil laminate tray containing a desiccant sachet and the tray is sealed with a peelable foil lid, which together, with the desiccant provides moisture protection. The lid should only be opened when the inhaler is ready to be used for the first time. Once the tray is opened, the desiccant package should be discarded.

Patients should be instructed to write the date the inhaler should be discarded on the label in the space provided. The date should be added as soon as the inhaler has been removed from the tray.

ARNUITY ELLIPTA should be safely discarded when the dose counter reads “0” or 6 weeks after it was removed from the foil tray, whichever comes first.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ARNIVITY ELLIPTA consists of an inhaler with a plastic light grey body, dose counter and orange mouthpiece cover. The inhaler encompasses a foil strip with 14 or 30 blisters. Each blister contains a white powder mixture of micronized fluticasone furoate (100 mcg or 200 mcg) and lactose monohydrate (to 12.5 mg) for inhalation administration. The lactose monohydrate contains milk proteins.

The actual amount of drug delivered to the lungs will depend on patient factors, such as inspiratory flow rate and inspiratory time.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

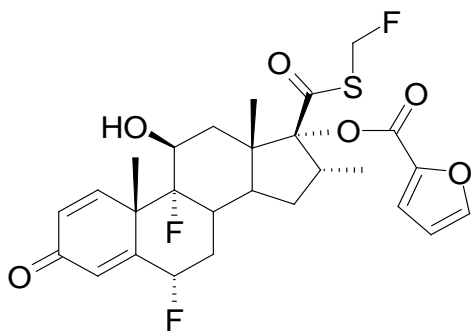
Drug Substance

Proper name: fluticasone furoate

Chemical name: (6 α ,11 β ,16 α ,17 α)-6,9-difluoro-17-[[[(fluoromethyl)thio]carbonyl]-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furancarboxylate

Molecular formula and molecular mass: C₂₇H₂₉F₃O₆S 538.6

Structural formula:



Physicochemical properties: fluticasone furoate is a white powder. It is practically insoluble in water.

CLINICAL TRIALS

Trial Design and Demographics

The efficacy of ARNUITY ELLIPTA 100 mcg and 200 mcg in the treatment of asthma has been evaluated in four randomized, double blind, parallel-group clinical trials of between 12 and 24 weeks in duration (FFA112059, HZA106827, FFA114496 and HZA106829) in patients aged 12 years and older with persistent asthma. These pivotal trials were designed to evaluate the efficacy of ARNUITY ELLIPTA 100 mcg and 200 mcg, 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 long-acting beta₂-adrenergic agonist (LABA).

Two of these studies (FFA112059 and HZA106829) included a comparator group in order to compare the relative benefits of ARNUITY ELLIPTA with the established inhaled corticosteroid fluticasone propionate.

Study treatments were delivered as inhalation powders. The primary endpoint in all pivotal trials was change from baseline in evening trough FEV₁ measured approximately 24 hours after the final dose of study medication. Trough FEV₁ (assessed at approximately 24 hours after the previous dose) was also assessed at clinic visits throughout the trials. Studies HZA106827 and HZA106829 had a co-primary endpoint of change from baseline in weighted mean serial FEV₁ 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 in a subset of patients. Details of the design and patient demographics of the pivotal trials are described in Table 5.

Table 5 Summary of Trial Design and Patient Demographics for Pivotal Trials

Study #	Trial Design, Route of Administration and Study Duration	Treatment and Dosage	Study Subjects Mean Age (Range) Gender (%)	Primary Efficacy Endpoint(s)
FFA112059	24 week, multicenter, randomized, placebo-controlled (with rescue medication) double-blind, double-dummy, parallel group study to evaluate the efficacy and safety of FF 100 mcg administered once-daily in the evening in adolescent and adult subjects 12 years of age and older with persistent bronchial asthma.	FF 100 mcg OD FP 250 mcg BD Placebo	Total:343 40.6 years (12-84) Male: 41% Female: 59%	Trough FEV ₁ at Week 24
HZA106827	12 week, multicenter, stratified, randomized, double-blind, placebo-controlled (with rescue medication), parallel group study to compare the efficacy and safety of FF/VI 100/25 mcg and FF 100 mcg both administered once-daily in the evening in adolescent and adult subjects 12 years of age and older with persistent bronchial asthma.	FF 100 mcg OD FF/VI 100/25 mcg OD Placebo	Total: 609 39.7 years (12-84) Male: 42% Female: 58%	Trough FEV ₁ at Week 12 Weighted mean FEV ₁ (0-24 hours) at Week 12
FFA114496	24 week, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of inhaled FF 100 mcg and 200 mcg administered once-daily in the evening in adolescent and adult subjects 12 years of age and older with persistent asthma.	FF 100 mcg OD FF 200 mcg OD	Total: 238 45.9 years (12-76) Male: 33% Female: 67%	Trough FEV ₁ at Week 24
HZA106829	24 week, multicenter, stratified, randomized, double-blind, double-dummy, parallel group, active controlled study to compare the efficacy and safety of FF/VI 200/25 mcg administered once-daily each evening to FF 200 mcg administered alone once-daily each evening in adolescent and adult subjects 12 years of age and older with persistent bronchial asthma.	FF 200 mcg OD FF/VI 200/25 mcg OD FP 500 mcg BD	Total: 586 46.2 years (12-76) Male: 41% Female: 59%	Trough FEV ₁ at Week 24* Weighted mean FEV ₁ (0-24 hours) at Week 24

Notes:

FF: fluticasone furoate; FP: fluticasone propionate; VI: vilanterol; OD: once-daily; BD: twice-daily

*FF vs. FP comparison was performed only for Trough FEV₁

Study Results

FFA112059 evaluated the efficacy of ARNUITY ELLIPTA 100 mcg once-daily and fluticasone propionate 250 mcg twice-daily on lung function in subjects with asthma compared to placebo. The trial included a 4-week run-in period during which subjects were symptomatic while taking their usual low to mid-dose inhaled corticosteroid therapy (i.e. fluticasone propionate 100 mcg to 500 mcg daily or equivalent). Mean baseline percent predicted FEV₁ 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.

Compared with placebo, at Week 24, the change from baseline in trough FEV₁ was significantly greater for ARNUITY ELLIPTA 100 mcg once-daily (146 mL) and for fluticasone propionate 250 mcg twice-daily (145 mL) (Table 6). Further, subjects receiving ARNUITY ELLIPTA 100 mcg once-daily had a statistically significantly greater improvement from baseline in percentage of 24-hour periods without the need of beta₂-agonist rescue medication use than subjects receiving placebo (treatment difference 14.8%, 95% CI: 6.9, 22.7, p<0.001, which equates to an additional 1 day per week without need for rescue medication).

Table 6 Statistical Analysis of Change from Baseline in Trough FEV₁ (mL) at Week 24 (FFA112059, ITT Population)

Trough FEV ₁ (mL) at Week 24	Placebo (n=113)	ARNUIITY ELLIPTA 100 mcg OD (n=111)	Fluticasone Propionate 250 mcg BD (n=107)
Least Squares Mean	2,372	2,519	2,517
Least Squares Mean Change from Baseline (SE)	15 (39.4)	161 (39.8)	159 (40.6)
Comparison vs. Placebo			
Difference		146	145
95% CI		36, 257	33, 257
p-value		0.009	0.011

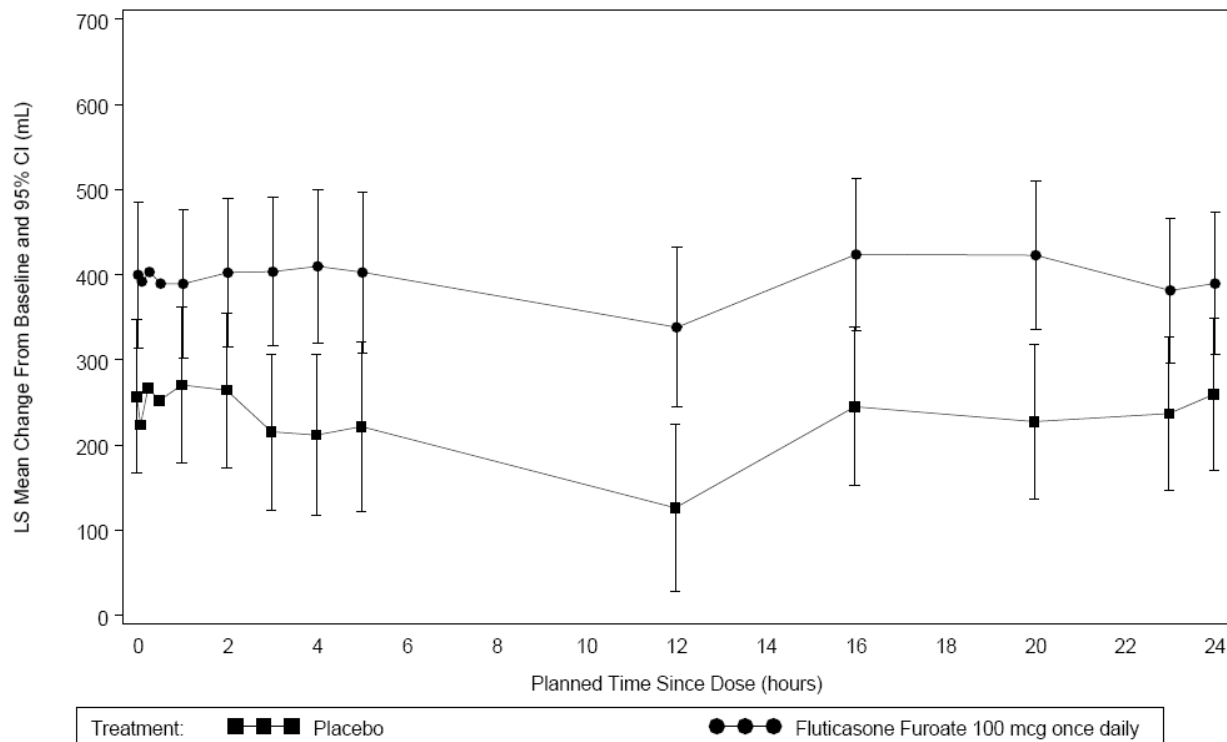
Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment

HZA106827 evaluated the efficacy of ARNUITY ELLIPTA 100 mcg once-daily in the evening 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. 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, (i.e. fluticasone propionate 200 mcg/day to 500 mcg/day or equivalent). LABA use was discontinued during the run-in. Mean baseline percent predicted FEV₁ 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.

ARNUIITY ELLIPTA 100 mcg once-daily had greater changes from baseline than placebo throughout the study. At Week 12, the change from baseline in trough FEV₁ for ARNUITY ELLIPTA 100 mcg once-daily was significantly greater than placebo (136 mL, 95% CI: 51, 222, p=0.002). At Week 12, the change from baseline in weighted mean FEV₁ (measured in a subset of patients (n=201)) was significantly greater for ARNUITY ELLIPTA 100 mcg compared with placebo (186 mL; 95% CI: 62, 310, p=0.003).

Lung function improvements were sustained over 24 hours (Figure 1).

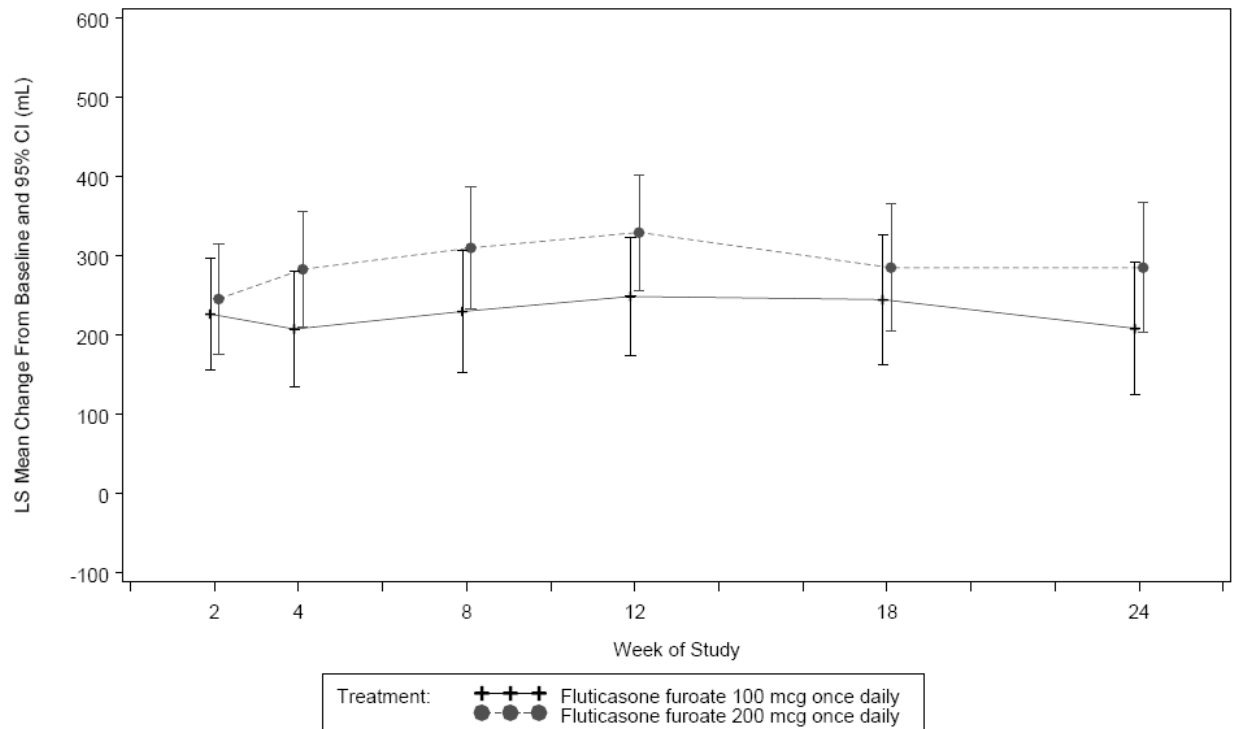
Figure 1 Change from Baseline in Individual Serial FEV₁ (mL) Assessments after 12 Weeks of Treatment (HZA106827)



FFA114496 evaluated the relative efficacy of ARNUITY ELLIPTA in doses of 100 mcg and 200 mcg on lung function in patients with asthma. 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 250 mcg/day to 1,000 mcg/day or equivalent). LABA use was discontinued during the run-in period. Mean baseline percent predicted FEV₁ was approximately 68% overall and similar in the two treatment groups. About 16% of subjects on ARNUITY ELLIPTA 100 mcg and 13% of subjects on ARNUITY ELLIPTA 200 mcg failed to complete the 24-week trial.

The group receiving ARNUITY ELLIPTA 200 mcg had generally numerically greater changes from baseline than the group receiving ARNUITY ELLIPTA 100 mcg throughout the study (Figure 2). At Week 24, the change from baseline in trough FEV₁ was 208 mL for ARNUITY ELLIPTA 100 mcg and 284 mL for ARNUITY ELLIPTA 200 mcg, a difference of 77 mL (95% CI: -39, 192).

Figure 2 Change from Baseline in Trough FEV₁ (mL) Over Time (FFA114496)

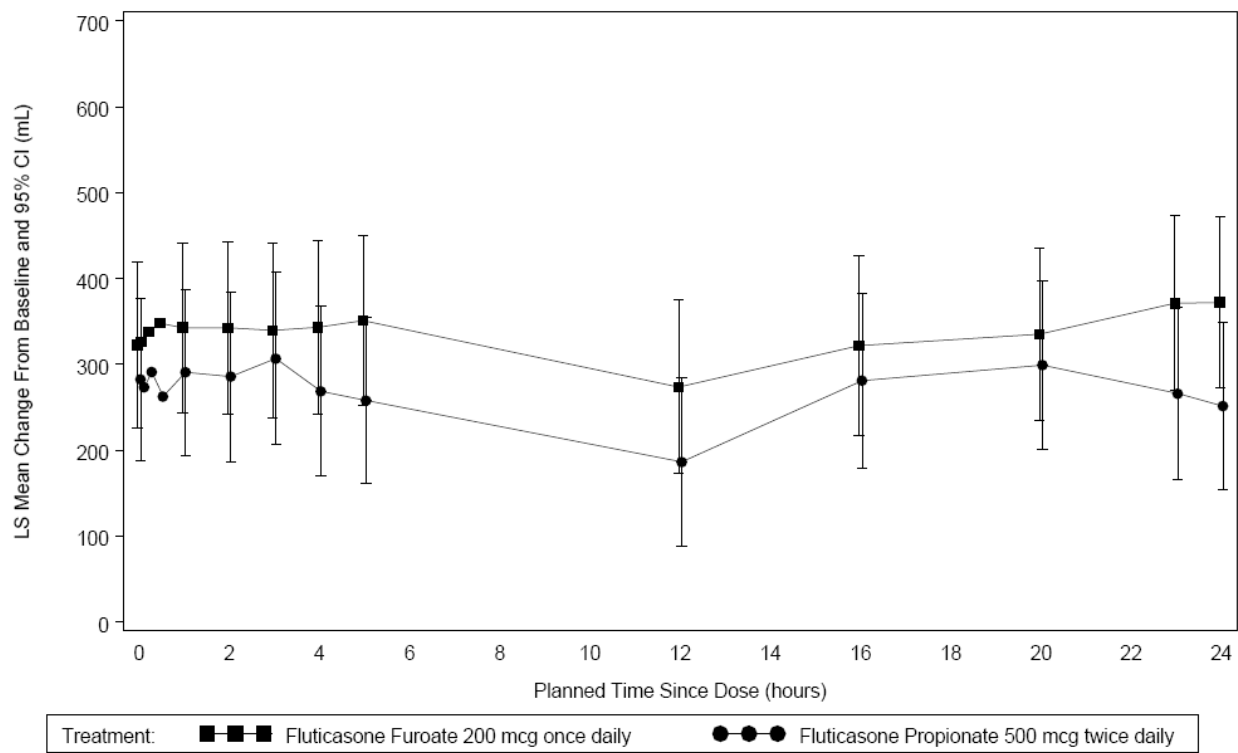


HZA106829 evaluated the efficacy of ARNUITY ELLIPTA 200 mcg once-daily in the evening, and fluticasone propionate 500 mcg twice-daily on lung function in subjects with asthma. The combination of fluticasone furoate 200 mcg and vilanterol 25 mcg was also included as a treatment arm. The trial included 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 mcg/day to 1,000 mcg/day or equivalent). LABA use was discontinued during the run-in period. Mean baseline percent predicted FEV₁ was approximately 67% in both treatment groups.

Similar improvements from baseline in lung function were observed for both ARNUITY ELLIPTA 200 mcg once-daily and fluticasone propionate 500 mcg twice-daily. At Week 24, the change from baseline in trough FEV₁ 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 24 hours as seen by change in weighted mean FEV₁ (Figure 3). At Week 24, the change from baseline in weighted mean FEV₁ (measured in a subset of patients (n=169)) was 328 mL for ARNUITY ELLIPTA 200 mcg once-daily and 258 mL for fluticasone propionate 500 twice-daily (treatment difference of 70 mL; 95% CI: -67, 208).

Figure 3 Change from Baseline in Individual Serial FEV₁ (mL) Assessments after 24 Weeks of Treatment (HZA106829)



DETAILED PHARMACOLOGY

Animal Pharmacology

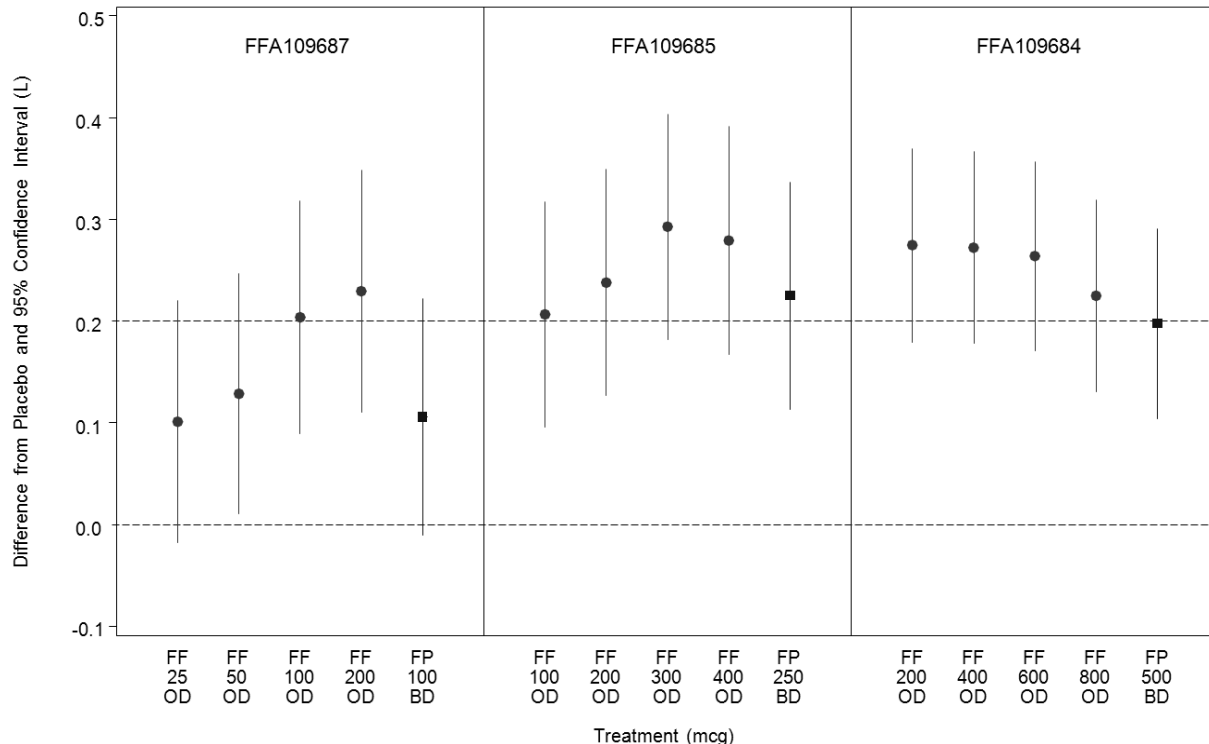
Pharmacological and toxicological effects seen with fluticasone furoate in nonclinical studies were those typically associated with glucocorticoids.

Clinical Pharmacology

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 (FFA109687, FFA109685, and FFA109684). Across the 3 trials, subjects were uncontrolled at baseline on treatments of short-acting beta₂-agonist and/or non-inhaled corticosteroid controller medications (FFA109687), low-dose inhaled corticosteroid (FFA109685), or medium doses of inhaled corticosteroid (FFA109684). The trials in Figure 4 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 FEV₁ 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 4.

Figure 4 Dose-Ranging Trials



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

To evaluate dosing frequency, a separate trial (FFA112202) 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 of this trial supported the selection of the once-daily dosing frequency.

TOXICOLOGY

Fluticasone furoate (FF) has undergone a comprehensive toxicological evaluation, and the principal findings are summarized in Table 7. In the majority of studies, fluticasone furoate was administered by the inhaled route which resulted in systemic exposure. The major findings were typically associated with systemic exposure to glucocorticoids, and are commonly reported for other marketed inhaled corticosteroids. In patients following repeated inhaled doses of 100 or 200 mcg/day plasma concentrations of fluticasone furoate were typically lower than those achieved in animal toxicology studies (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Table 7 Summary of Principal Findings in Fluticasone Furoate Toxicology Studies

Study Type & Duration	Route	Species	Dose mcg/kg/day (unless indicated)	Noteworthy Findings	
Single Dose	oral	mouse	1000, 1500, 2000 (mg/kg)	Findings following high single doses included reduced body weight and lymphoid depletion. Gastric irritation was seen following high dose oral administration in rats.	
	intravenous inhalation		18000, 30000 7100		
oral	rat	1000, 1500, 2000 (mg/kg)			
intravenous inhalation		12000, 18000 4400			
^a Repeat Dose 4 weeks	inhalation	rat	6.9, 17.6, 71.7 6.5, 19.5, 72.0	Findings following repeated inhalation administration of FF included suppressed weight gain, lymphocytopenia, reduced adrenal weight/cortical atrophy, decreased cellularity of lymphoid tissues, and hypocellularity/prominent adipocytes in bone marrow. In dogs, reduced plasma cortisol, increased hepatic glycogen and infection secondary to immunosuppression were observed, along with development of Cushingoid syndrome on chronic treatment. In all species, there was no evidence of significant treatment related effects on the respiratory tract.	
		dog	10.6, 30.6, 105 9, 22, 74		
	13 weeks	inhalation	mouse		7.3, 18.6, 76.9
		rat	4.3, 8.5, 24.3		
		dog	11.3, 33.0, 64.7		
26 weeks	inhalation	rat	3.2, 8.3, 20.3		
39 weeks	inhalation	dog	13.3, 30.1, 59.6		
Repeat Dose 14 days	intranasal	rat (male)	80, 160 (mcg/day)	In intranasal studies, findings following administration of FF were similar to those seen following inhalation administration. In the 26 week dog study, local effects were confined to increased numbers of goblet cells in the nasal epithelium, considered an adaptive response to local administration of supratherapeutic levels of FF.	
	intranasal	dog	400, 1200 (mcg/day)		
	intranasal	dog	1200, 2400 (mcg/day)		
Genotoxicity AMES Mouse lymphoma	<i>In vitro</i>	NA*	up to 1000 (mcg/plate) up to 25 (mcg/mL)	FF did not cause gene mutation in bacteria or chromosomal damage in mammalian cells <i>in vitro</i> .	
Micronucleus (2 doses, 24 hours apart)	intravenous	rat	625, 1000 1000, 2000, 4000 10000, 20000, 40000	There was no evidence of genotoxicity in the <i>in vivo</i> micronucleus tests in rats.	
Carcinogenicity 104 weeks	Inhalation	mouse	2.2, 6.1, 18.8	There was no evidence of treatment-related increases in tumour incidence in two year inhalation studies in rats and mice.	
		rat	1.0, 3.2, 8.6		

Study Type & Duration	Route	Species	Dose mcg/kg/day (unless indicated)	Noteworthy Findings
Reproductive Toxicity Male fertility 69 to 73 days (from 28 days prior to co-habitation)	inhalation	rat	6.6, 12.9, 29.4	There were no effects on mating performance or fertility of male or female rats. Developmental toxicity in rats was confined to an increased incidence of incompletely ossified sternabrae in association with lower fetal weight. High doses in rabbits (46.6 mcg/kg/day) induced abortion. There were no major skeletal or visceral abnormalities in either rats or rabbits, and no effect on pre- or post-natal development in rats treated with FF during gestation and lactation.
FFEEFD** 41 to 46 days (from 14 days prior to mating until Day 17 of pregnancy)	inhalation	rat	11, 23, 91	The developmental NOAEL in female rats achieved systemic exposures approximately 4-fold greater than in patients with asthma receiving FF 200 mcg/day ^b ; this dose is similar to the NOAEL in the male fertility and PPN studies in which TK data were not collected; AUC data for the NOAEL could not be calculated for the rabbit EFD study, but, at NOAEL, C _{max} was approximately 2-fold greater than in patients with asthma receiving FF, 200 mcg/day ^b .
EFD*** 13 days (from Days 8 to 20 of pregnancy)	inhalation	rabbit	9.7, 46.6, 85.1 1.8, 3.2, 8.1	
PPN**** 35 days (from Days 6 to 20pc and Days 2 to 21pp)	inhalation	rat	5.5, 15.7, 27.2	
Juvenile***** (up to 13 weeks)	inhalation,	rat,	7.9, 27, 73 41.8	
		dog	9.8, 27, 73 59.9	In juvenile rats and dogs findings were consistent with the corticosteroid effects of FF seen in adult animals. Although the majority of changes were also seen in inhalation toxicity studies in adult animals, some findings in kidney, eyes, bone, lungs and teeth associated with FF treatment, were only seen in juvenile dogs dosed for 13 weeks.
14 days	intranasal	dog	800 (µg/day)	
Local Tolerance Dermal irritancy 4 hours 16 hours	topical	rabbit	500 (mcg) 0.2 (mcg/mL)	FF was non-irritating following single dose application to the skin, and practically non-irritating following application of the intranasal clinical formulation to the eye.
Ocular irritancy Single dose	topical	rabbit	0.05% (w/w)	
Other Toxicity Respiratory hypersensitivity 5 days	inhalation	guinea pig (male)	67.1 to 71.2	There was no evidence of respiratory hypersensitivity reactions following inhalation administration of FF.

Study Type & Duration	Route	Species	Dose mcg/kg/day (unless indicated)	Noteworthy Findings
<p>Key:</p> <p>*NA = Not applicable</p> <p>**FFEEFD = Female fertility, early embryonic and embryofoetal development</p> <p>*** EFD = Embryofoetal development</p> <p>**** PPN =Pre- and post-natal development</p> <p>***** Juvenile At start of dosing juvenile rats were aged approximately 21 days and juvenile dogs were aged approximately 8 weeks.</p> <p>pc = post-coitum</p> <p>pp = post partum</p> <p>a = In all species, corticosteroid-related findings in repeat-dose toxicity studies with FF occurred at all doses, thus, a NOEL/NOAEL was not identified.</p> <p>b = Estimated geometric mean systemic exposure following administration of 200 mcg FF single strip in subjects with asthma = 0.0551 ng/mL (C_{max}) or 0.395 ng.h/mL (AUC)</p>				

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PART III: CONSUMER INFORMATION

ARNUIITY ELLIPTA fluticasone furoate dry powder for oral inhalation

This leaflet is part III of a three-part "Product Monograph" published when ARNUITY ELLIPTA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ARNUITY ELLIPTA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ARNUIITY ELLIPTA is an inhaled corticosteroid used for the long-term treatment of asthma in people aged 12 years and older.

What it does:

ARNUIITY ELLIPTA contains fluticasone furoate. Fluticasone furoate is an inhaled corticosteroid. It reduces inflammation in the airways of the lungs, which can ease breathing problems.

This medicine does not cure asthma but helps to prevent and control its symptoms.

When it should not be used:

Do not use ARNUITY ELLIPTA:

- To treat sudden symptoms of asthma. **ARNUIITY 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 salbutamol, during a sudden asthma attack.
- If you are allergic to any of the medicinal or nonmedicinal ingredients contained in the product;
- If you have a lactose or severe milk protein allergy.
- If you are under 12 years of age.

What the medicinal ingredient is:

Fluticasone furoate.

What the nonmedicinal ingredients are:

Lactose monohydrate (which contains milk proteins).

What dosage forms it comes in:

Dry Powder for Oral Inhalation: 100 mcg and 200 mcg

The dry powder is contained in a series of separate blisters and is delivered by the ELLIPTA inhaler.

Each inhaler contains 30 doses (one inhalation per day for 30 days).

If a sample is given to you by your doctor, it will contain 14 doses (one inhalation per day for 14 days).

WARNINGS AND PRECAUTIONS

BEFORE you use ARNUITY ELLIPTA talk to your doctor or pharmacist if you:

- have liver disease, as you may be more likely to have side effects;
- have weak bones (osteoporosis)
- have eye problems such as glaucoma or cataracts
- are pregnant or planning to become pregnant
- are breastfeeding
- have ever had thrush or a yeast infection in your mouth;
- have ever had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems;
- have been taking other corticosteroids by mouth or inhalation;
- have an immune system problem;
- have ever had herpes simplex of the eye, a history of tuberculosis infections, or any type of viral, bacterial, fungal (yeast), or parasitic infection.

If you have moderate to severe liver problems, your doctor may do blood tests to monitor your liver function.

If you experience sudden shortness of breath or wheezing, or develop any other symptoms of an asthma attack, you should use your rapid onset, short duration, inhaled bronchodilator (e.g., salbutamol) and seek medical attention.

You should avoid coming into contact with people who have measles or chicken pox while taking ARNUITY ELLIPTA. If you are exposed, tell your doctor right away.

Drugs like ARNUITY ELLIPTA can cause Eye Disorders:

- Cataracts: clouding of the lens in the eye, blurry vision, eye pain;
- Glaucoma: An increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss;
- You should therefore have regular eye exams.

Pregnancy:

ARNUITY ELLIPTA is not usually recommended for use during pregnancy.

Before prescribing ARNUITY ELLIPTA your doctor will consider the benefit to you and the risk to your unborn baby.

Breastfeeding/Lactation:

It is not known whether the ingredients of ARNUITY ELLIPTA can pass into breast milk. If you are breastfeeding, **check with your doctor** before you take ARNUITY ELLIPTA.

Tell your doctor immediately if:

- There is a change in your symptoms such as more coughing, attacks of wheezing, chest tightness, or an unusual increase in the severity of the breathlessness.
- You wake up at night with chest tightness, wheezing or shortness of breath.
- You are using increasing amounts of your rescue inhaler.

These could be warning signs that your condition may be worsening

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with ARNUITY ELLIPTA include:

- Ketoconazole used to treat fungal infections;
- Anti-HIV medicines;
- Clarithromycin used to treat bacterial infections;
- Any other corticosteroid medicines.

PROPER USE OF THIS MEDICATION

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.

Your doctor will determine the dose of ARNUITY ELLIPTA based on the severity of your asthma and if you have liver disease.

It is important to continue using ARNUITY ELLIPTA even if you do not have any symptoms.

Do not stop taking ARNUITY ELLIPTA without talking to your doctor.

Take ARNUITY ELLIPTA:

- exactly as prescribed;
- every day;
- every 24 hours, at about the same time each day

Rinse your mouth with water after each inhalation. Do not swallow the water

Usual dose: One inhalation through the mouth once a day.

If you have severe asthma, your doctor may decide that you should use the higher strength of ARNUITY ELLIPTA (200 mcg).

If you have liver disease, your doctor may decide that you should use the lower strength of ARNUITY ELLIPTA (100 mcg).

Do not take more than the recommended dose.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

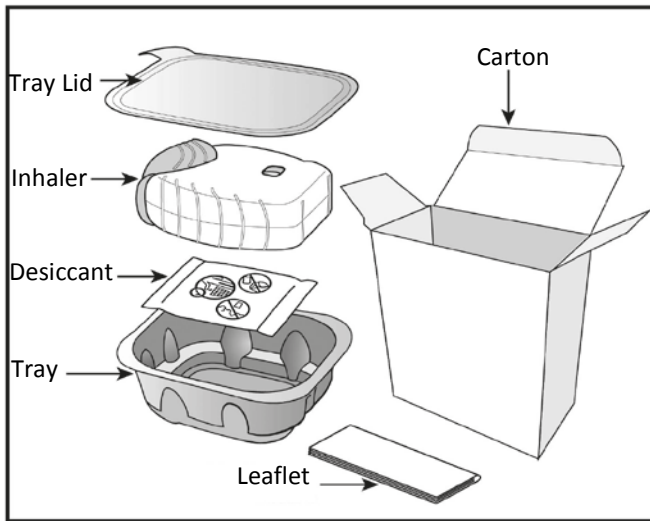
If you have taken larger doses than instructed for a long period of time, you should ask your doctor or pharmacist for advice.

Missed Dose:

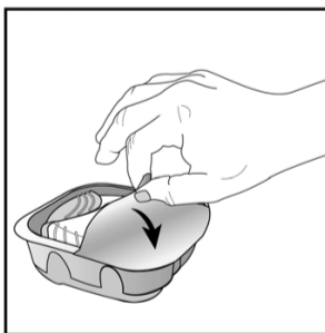
If you miss a dose, carry on and take your next dose at the usual time the next day. **Do not** take an extra dose to make up for the missed one.

About your ARNUITY ELLIPTA Inhaler:

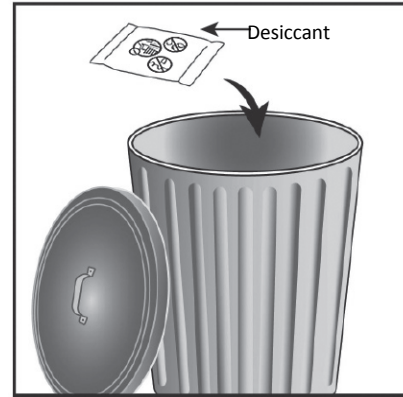
Your ELLIPTA inhaler carton contains:



The plastic ELLIPTA inhaler is packaged in a tray, with a peelable foil lid. **Do not remove the foil until you are ready to use the inhaler.** Peel back the lid to open the tray.



In the tray, you will find a small desiccant sachet containing a drying agent. The desiccant sachet helps to prevent moisture from forming inside the tray. **Keep it away from children and pets. Throw away the desiccant sachet** once you have opened the lid of the tray. It is dangerous to eat or inhale the contents of the desiccant sachet.



When you take your ELLIPTA inhaler out of its tray it will be in the closed position. Write the “Discard by” date on the inhaler label in the space provided. The “Discard by” date is 6 weeks from the date you open the tray.

The plastic ELLIPTA inhaler has a light grey body, an orange mouthpiece cover, and a dose counter. The mouthpiece and the air vent are hidden by the cover and can only be seen when the cover is opened. The ELLIPTA inhaler is ready-to-use. You will not need to prime it before using it for the first time.

Cover

Each time you open this, you prepare one dose of medicine.

Dose Counter

This shows how many doses of medicine are left in the inhaler.

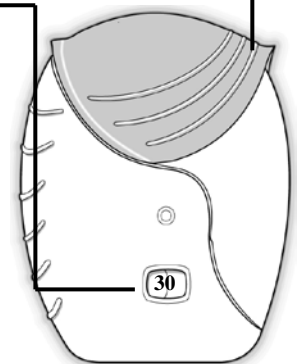
Before the inhaler has been used, it shows exactly 30 doses (14 for sample and hospital packs).

It counts down by 1 each time you open the cover.

When fewer than 10 doses are left, half of the dose counter shows red to remind you to refill your prescription.

After you have inhaled the last dose, the counter shows 0. Your inhaler is now empty.

If you open the cover after this, the dose counter will change from half red to completely red.



IMPORTANT:

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

Never try to alter the numbers on the counter or detach the counter on the front of the ELLIPTA inhaler. The counter cannot be reset and is permanently attached to the inhaler.

How to use ARNUITY ELLIPTA:

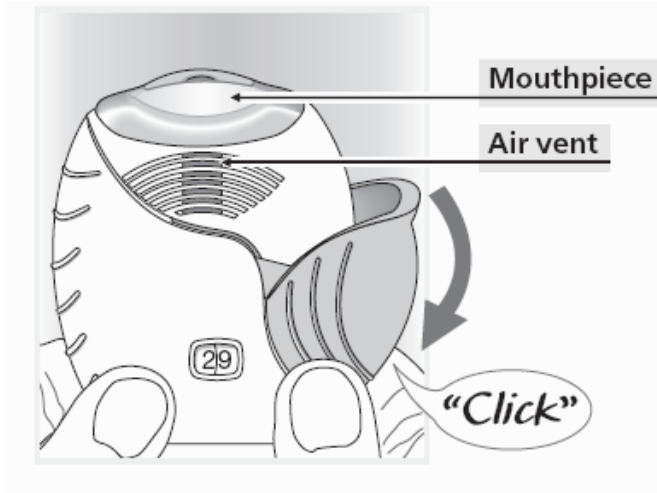
Please follow the instructions ‘**OPEN, INHALE, and CLOSE**’ to use your ELLIPTA inhaler. The instructions shown below apply to both the 30-dose and 14-dose ELLIPTA inhaler.

Keep the cover closed until you are ready to inhale a dose. Do not shake the ELLIPTA inhaler at any point during use as this is not necessary.

Sit down or stand in a comfortable position.

OPEN:

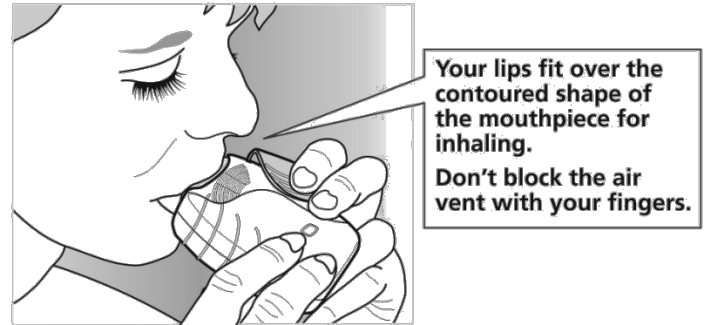
1. When you are ready, activate the inhaler by sliding the orange cover down until you hear a ‘click’ to prepare a dose.
2. The dose counter will now count down by one number (“1”). *It is unlikely the dose counter will not count down as you hear the ‘click’.* If this happens, it may mean the inhaler did not load the medicine. Bring it back to your pharmacist for advice.
3. While holding the inhaler away from your mouth, exhale a complete breath (i.e. breathe out as far as is comfortable). *Don’t breathe out into the inhaler.*



You are now ready to inhale a dose.

INHALE:

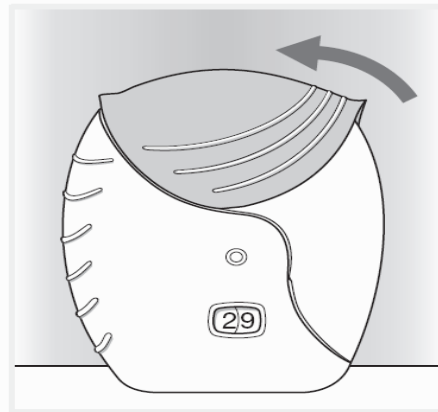
1. Put the mouthpiece between your lips, and close your lips firmly around it. *Don’t block the air vent with your fingers.*



2. Take one long, steady, deep breath in. Hold this breath for as long as possible (minimum 3-4 seconds).

CLOSE:

1. Remove the inhaler from your mouth. Exhale slowly and gently. Continue to breathe normally.
2. You can clean the mouthpiece of the inhaler with a clean dry tissue after you have inhaled the medicine.
3. Close the inhaler by sliding the cover upwards as far as it will go to cover the mouthpiece.



You may not be able to taste or feel the medicine (this is normal), even when you are using the inhaler correctly.

4. Rinse your mouth with water. **Do not** swallow.



SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Sore, raised patches in the mouth or throat caused by a yeast infection (*candidiasis*/thrush). After using ARNUITY ELLIPTA, rinse your mouth out with water immediately (do not swallow) as it may help stop this side effect from occurring.
- Infection or inflammation of the nose or throat
- Feeling of pressure or pain in the cheeks and forehead (may be signs of inflammation of the sinuses called sinusitis)
- Pain and irritation in the back of the mouth and throat
- Headache
- Back pain
- Cough
- Hoarseness and voice changes
- Respiratory tract infection
- Stomach pain and diarrhea

If any of these affects you severely, tell your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Thrush (yeast infection): White patches in the mouth and on the tongue, sore throat		✓	
	Bronchitis (inflammation of the lungs).		✓	
	Flu: sore throat, fever, headache, sore muscles, cough		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Unknown	Pneumonia (an infection of the lungs): Fever, chills, increase in sputum production, change in sputum colour, increased cough or an increase in breathing difficulties (shortness of breath, chest pain).		✓	
	Asthma exacerbations		✓	
	Decreased Adrenal Function: Tiredness, weakness, nausea and vomiting, low blood pressure.		✓	
	Glaucoma: New or worsened pressure in your eyes, eye pain or discomfort, blurred vision, seeing halos or rainbows around items or red eyes		✓	
	Cataract: clouding of the lens in the eye, blurry vision and/or eye pain.		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
<p>Allergic Reaction: Skin rash, hives, redness, swelling of the face, lips, tongue or throat (angioedema), becoming very wheezy, coughing or difficulty swallowing or breathing, suddenly feeling weak or light headed (may lead to collapse of consciousness).</p>			✓
<p>Bone Fractures or Osteoporosis: In situations where healthy people would not normally break a bone you may have sudden pain in any location and especially in the wrist, spine or hip. This may be a fracture.</p>		✓	

This is not a complete list of side effects. For any unexpected effects while taking ARNUITY ELLIPTA contact your doctor or pharmacist.

HOW TO STORE IT

- **Keep out of the reach and sight of children. Your medicine may harm them.**
- **Keep your inhaler in a cool dry place away from direct heat or sunlight.** Keep it closed when not in use.
- Do not store ARNUITY ELLIPTA above 25°C. If you store in a refrigerator, **allow the inhaler to return to room temperature for at least an hour** before use.
- Store in the original package container in order to protect from moisture and do not open the foil lid until ready for first use.
- Once the tray is opened:
 - You can use the inhaler for up to 6 weeks, starting from the date you opened the lid of the tray.
 - Write the date the inhaler should be discarded on the inhaler in the space provided.
- Safely discard ARNUITY ELLIPTA when the dose counter reads “0” or 6 weeks after you open the lid of the tray, whichever comes first. **ARNUITY ELLIPTA expires 6 weeks after you have opened the lid of the tray.**

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: **Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

You may need to read this package insert again. **Please do not throw it away** until you have finished your medicine.

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.gsk.ca> or by contacting the sponsor, GlaxoSmithKline Inc., at:
7333 Mississauga Road
Mississauga, Ontario
Canada L5N 6L4
1-800-387-7374

This leaflet was prepared by GSK Inc.

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