AUSTRALIAN PRODUCT INFORMATION

ARNUITY ELLIPTA

1. NAME OF THE MEDICINE

Fluticasone furoate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each foil strip contains regularly distributed blisters containing 50, 100 or 200 micrograms of fluticasone furoate.

Excipients with known effect:

Lactose monohydrate (which contains milk protein). There are 12.5 milligrams of lactose monohydrate per dose.

For the full list of excipients see section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Powder for inhalation

White powder in a light grey inhaler (Ellipta) with a pale orange mouthpiece cover and a dose counter.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ARNUITY ELLIPTA is indicated for the maintenance treatment of asthma in patients aged ≥5 years.

4.2 DOSE AND METHOD OF ADMINISTRATION

ARNUITY ELLIPTA is for oral inhalation only.

ARNUITY ELLIPTA should be administered once daily either morning or evening but at the same time every day.

Do not use ARNUITY ELLIPTA more than once every 24 hours. If symptoms arise between doses, an inhaled short-acting beta$_2$-agonist should be used for immediate relief. The starting dosage for ARNUITY ELLIPTA is based upon patients' asthma severity and age. After inhalation, the patient should rinse their mouth with water without swallowing.

Patients should be made aware that fluticasone furoate must be used regularly, even when asymptomatic.

Patients should be regularly reassessed by a healthcare professional so that the dose of fluticasone furoate they are receiving remains optimal and is only changed on medical advice.

To minimise adverse reactions, inhaled corticosteroids should be used at the lowest dose that maintains symptom control.

Prescribers should be aware that fluticasone furoate is a novel inhaled corticosteroid with different dosing requirements to older inhaled corticosteroids including fluticasone propionate.

Dose

Adults and adolescents aged 12 years and over

100 or 200 micrograms of ARNUITY ELLIPTA once daily.

The usual recommended starting dose for patients not on an inhaled corticosteroid is 100 micrograms. 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 micrograms, replacement with ARNUITY ELLIPTA 200 micrograms may provide additional asthma control.

Children aged 5 to less than 12 years

One inhalation of ARNUITY ELLIPTA 50 micrograms once daily.

Children aged less than 5 years

ARNUITY ELLIPTA should not be used in children younger than 5 years of age.

The safety and efficacy of ARNUITY ELLIPTA have not been established in children less than 5 years of age.

Special populations

Elderly

No dosage adjustment is required in patients over 65 years (see section 5.2 PHARMACOKINETIC PROPERTIES – Special Patient Populations).

Renal impairment

No dose adjustment is required for patients with renal impairment (see section 5.2 PHARMACOKINETIC PROPERTIES – Special Patient Populations).

Hepatic Impairment

A clinical pharmacology study in adult subjects with mild, moderate and severe hepatic impairment showed up to 3-fold increase in systemic exposure to fluticasone furoate

(AUC) (see section 5.2 PHARMACOKINETIC PROPERTIES – Special Patient Populations).

Caution should be exercised when dosing patients with hepatic impairment who may be more at risk of systemic adverse reactions associated with corticosteroids.

For patients aged 12 and older with moderate or severe hepatic impairment, the maximum daily dose is 100 micrograms once daily. (see section 5.2 PHARMACOKINETIC PROPERTIES – Special Patient Populations).

Fluticasone furoate has not been studied in children under 12 years of age with hepatic impairment. Therefore, the use of ARNUITY ELLIPTA is not recommended in children under 12 years of age with hepatic impairment.

4.3 CONTRAINDICATIONS

ARNUITY ELLIPTA is contraindicated in patients with severe milk-protein allergy or who have demonstrated hypersensitivity to fluticasone furoate or lactose.

ARNUITY ELLIPTA is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Deterioration of Disease

ARNUITY ELLIPTA should not be used to treat acute asthma symptoms, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist.

Patients with asthma should have a personal action plan designed in association with their physician. Patients should not stop therapy with ARNUITY ELLIPTA without physician supervision since symptoms may recur after discontinuation.

Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

Paradoxical Bronchospasm

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

Systemic Corticosteroid Effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Ocular effects may be reported with systemic and topical corticosteroid use. If a patient presents with a change in vision, the patient should be considered for the referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR).

To minimise adverse reactions, inhaled corticosteroids should be used at the lowest dose that maintains symptom control. Patients should be assessed at regular intervals, including assessment of growth in children.

In patients whose asthma is well controlled and stable, the ARNUITY ELLIPTA dose should be down-titrated to the lowest strength of ARNUITY ELLIPTA.

Persons using drugs that suppress the immune system are more susceptible to infections than healthy individuals. 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. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids and adequate prophylaxis and antiviral treatment should be considered.

Pneumonia

An increase in pneumonia has been observed in patients with Chronic Obstructive Pulmonary Disease (COPD) receiving inhaled corticosteroids. In studies in patients with asthma, no difference was observed in the incidence of pneumonia with fluticasone furoate 100 micrograms compared to placebo. An increased incidence of pneumonia in asthmatic patients with higher doses of inhaled corticosteroids cannot be excluded.

HPA Axis Suppression and Adrenal Insufficiency

ARNUITY ELLIPTA will often help control asthma symptoms with less suppression of hypothalamic-pituitary-adrenal (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 (compared to oral corticosteroids), the beneficial effects of ARNUITY ELLIPTA in minimising HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 for evidence of inadequate adrenal response 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.

As with all inhaled corticosteroids, caution should be used when inhaled corticosteroids are used with other nasal corticosteroids, or medications that can alter the activity of hepatic enzymes.

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 (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 (symptoms include fatigue, lassitude, weakness, nausea and vomiting, and hypotension) 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 milligrams 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. 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.

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 section 4.3 CONTRAINDICATIONS).

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 immobilisation, 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.

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 minimise 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 section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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.

Use in the Elderly

There was no evidence for age (up to 84 years) to affect the pharmacokinetics of fluticasone furoate in subjects with asthma.

Paediatric Use

The safety and efficacy of ARNUITY ELLIPTA have not been established in children less than 5 years of age.

Effect on Laboratory Tests

Interactions with laboratory tests have not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Clinically significant drug interactions mediated by fluticasone furoate at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Interaction with CYP3A4 inhibitors

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

Care is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to fluticasone furoate, which could lead to an increase in the potential for adverse reactions (see section 5.2 PHARMACOKINETIC PROPERTIES).

Interaction with P-glycoprotein inhibitors

Fluticasone furoate is a substrate of P-gp. Clinical pharmacology studies with a specific P-gp inhibitor and fluticasone furoate have not been conducted (see section 5.2 PHARMACOKINETIC PROPERTIES).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There are no fertility data in humans. Studies in rats showed no effect of fluticasone furoate on male or female fertility.

Use in Pregnancy (Category B3)

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

Fluticasone furoate was not teratogenic in studies by the inhalational route in rats and rabbits, but it caused decreased fetal weight and impaired ossification in rats (at 91 micrograms/kilogram/day) and abortion in rabbits (at doses of 47 micrograms/kilogram/day and greater), occurring in conjunction with maternotoxicity. There were no adverse effects on embryofetal development in rats at 23 micrograms/kilogram/day, yielding systemic exposure approximately 4-times greater than that in patients at the maximum recommended human dose based on AUC, and there were no developmental effects in a prenatal and postnatal study in rats (at doses up to 27 micrograms/kilogram/day).

There has been limited pregnancy exposure in humans.

Administration of ARNUITY ELLIPTA to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Use in Lactation

There is no information on the excretion of fluticasone furoate or its metabolites in human milk, however, other corticosteroids are detected in human milk. A risk to breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue ARNUITY ELLIPTA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of fluticasone furoate driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of fluticasone furoate.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

The safety of ARNUITY ELLIPTA in adults and adolescents (aged 12 years and over) 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 micrograms. ARNUITY ELLIPTA 100 micrograms was studied in 1,663 subjects, and ARNUITY ELLIPTA 200 micrograms was studied in 608 subjects. Subject ages ranged from 12 to 84 years, 65% were female, and 75% were Caucasian.

The incidence of adverse events associated with ARNUITY ELLIPTA 100 micrograms is shown in Table 1 and is based on one 24-week trial (FFA112059) in adolescent and adult subjects with asthma.

Table 1. Adverse Events with ARNUITY ELLIPTA 100 micrograms with ≥3% Incidence and More Common than Placebo (FFA112059, Intent-to-Treat Population)

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

The incidence of adverse events associated with ARNUITY ELLIPTA 200 micrograms is shown in Table 2 and is based on one 24-week trial (FFA114496) in adolescent and adult subjects with asthma. This trial did not have a placebo arm.

Table 2. Adverse Events with ARNUITY ELLIPTA 200 micrograms with ≥3% Incidence (FFA114496, Safety Population)

Adverse Event	ARNUITY ELLIPTA 200 micrograms	ARNUITY ELLIPTA 100 micrograms
	(n=119)	(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 events observed in the other trials in adults and adolescents were consistent with those described in Tables 1 and 2.

The following adverse reactions were observed at a frequency of 3% or more, and higher than placebo, in adult and adolescent subjects receiving fluticasone furoate monotherapy in the key efficacy studies.

The following convention has been used for the classification of adverse reactions:

Very common:	≥1/10
Common:	≥1/100 to <1/10
Uncommon:	≥1/1000 to <1/100
Rare:	≥1/10000 to <1/1000
Very rare:	<1/10000

Table 3. Adverse Reactions with ARNUITY ELLIPTA listed by MedDRA system organ class and frequency

System organ class	Adverse reaction(s)	Frequency
Infections and infestations	Upper Respiratory Tract Infection, Bronchitis, Influenza Candidiasis of mouth and throat	Common
Nervous system disorders	Headache	Very Common
Respiratory, thoracic and mediastinal disorders	Nasopharyngitis	Very Common
	Oropharyngeal pain Sinusitis, Pharyngitis Cough	Common
Musculoskeletal and connective tissue disorders	Back pain	Common

The safety data for paediatric subjects is based upon one 12 week clinical trial that enrolled subjects with asthma aged 5 to younger than 12 years. Dosages of fluticasone furoate studied were 25, 50, or 100 micrograms administered once daily. ARNUITY ELLIPTA 50 micrograms was studied in 120 subjects (46 females and 74 males) (see section 5.1 PHARMACODYNAMIC PROPERTIES). Adverse reactions (≥ 3% and greater than placebo) seen in paediatric subjects were similar to those reported in adult and adolescent subjects. Adverse reactions occurring in ≥ 3% of subjects treated with ARNUITY ELLIPTA 50 micrograms and greater than placebo were bronchitis, pharyngitis, and viral infection.

Long-Term Safety

Long-term safety data is based on 2 trials in adolescent and adult subjects with asthma.

In one 12-month treatment trial subjects received, in combination with a long-acting beta$_2$-adrenergic agonist (LABA), fluticasone furoate 100 micrograms (n=201) or fluticasone furoate 200 micrograms (n=202). 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 micrograms or fluticasone furoate 200 micrograms included pyrexia, extrasystoles, upper abdominal pain, respiratory tract infection, diarrhea, and allergic rhinitis.

In the second long-term safety trial, subjects received fluticasone furoate 100 micrograms (n=1,010) for 24 to 76 weeks. 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 micrograms for up to 76 weeks included allergic rhinitis, nasal congestion, and arthralgia.

Post-marketing data

System organ class	Adverse reaction(s)	Frequency
Immune system disorders	Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria	Rare
Respiratory, thoracic and mediastinal disorders	Dysphonia	Rare

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms and signs

There are no data available from clinical trials on overdose with ARNUITY ELLIPTA.

An overdose of fluticasone furoate may produce signs and symptoms consistent with the known inhaled corticosteroid class effects (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Treatment

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. 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. eosinophils, macrophages, lymphocytes) and mediators (e.g. cytokines and chemokines) involved in inflammation.

An overall summary of PK/PD data from eight clinical pharmacology studies showed that administration of inhaled fluticasone furoate at repeat doses up to 400 micrograms was not associated with statistically significant decreases in serum cortisol (on average less than 20% decrease in serum cortisol). However this population average may not be representative of an individual's clinical response which will be influenced by individual differences in metabolism and tissue sensitivity following exposure to corticosteroids. A randomised, double-blind, parallel group trial in 104 paediatric subjects with asthma aged 5 to less than 12 years showed once daily treatment with fluticasone furoate 50 micrograms (n=104) to be non-inferior to placebo on serum cortisol weighted mean (0-24 h) and serum cortisol $AUC_{(0-24)}$ after 6-weeks of treatment.

Clinical Trials

<u>Adults and adolescents (aged 12 years and over)</u>

The efficacy of fluticasone furoate (FF) 100 micrograms and 200 micrograms in the treatment of asthma has been evaluated in 4 randomised, double blind, parallel-group clinical trials of between 12 and 24 weeks in duration (FFA112059, HZA106827, HZA106829 and FFA114496) and a further 8-week Phase IIb supportive study (FFA109687), in patients aged 12 years and older with persistent asthma. The trials were designed to evaluate the efficacy of FF 100 micrograms and 200 micrograms, given once daily in the evening, on lung function in subjects who were not controlled on their current treatments of non-corticosteroids (e.g. short-acting $beta_2$-adrenergic agonists (SABA), leukotriene modifiers), inhaled corticosteroids, or combination therapy consisting of an inhaled corticosteroid plus a LABA.

Three of these studies (FFA112059, HZA106829 and FFA109687) included a comparator group in order to compare the relative benefits of FF with the established inhaled corticosteroid fluticasone propionate (FP).

Studies in patients previously treated with inhaled corticosteroids or combination therapy

FFA112059 was a 24-week study which evaluated the efficacy of FF 100 micrograms once daily and FP 250 micrograms 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. FP 100 to 500 micrograms daily or equivalent). The primary endpoint was the change from baseline trough FEV_1 after the 24-week period. The groups receiving FF 100 micrograms once daily and FP 250 micrograms twice daily had greater changes from baseline in trough FEV_1 compared to the placebo group throughout the study.

The results of FFA112059 are shown in Table 4.

Table 4. Summary of Data from Study FFA112059

Trough FEV_1 (mL) at week 24	Placebo	FF 100 micrograms OD	FP 250 micrograms BD
	(n=113)	(n=111)	(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 against 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 was a 12-week study which evaluated the efficacy of FF 100 micrograms once daily in the evening on lung function in subjects with asthma against placebo. 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. FP 200 to 500 micrograms/day or equivalent). LABA use was discontinued during the run-in. The co-primary efficacy endpoints were change from baseline trough FEV_1 on week 12 and weighted mean FEV_1 (0-24 hr) on the last day of the 12-week treatment period. FF 100 micrograms once daily had greater changes from baseline than placebo throughout the study. At week 12, the change from baseline in trough FEV_1 for FF 100 micrograms once daily was significantly greater than placebo and lung function improvements were sustained over 24 hours. At week 12 the change from baseline in weighted mean FEV_1 was significantly greater for FF 100 micrograms compared with placebo.

The results of HZA106827 are shown in Tables 5 and 6.

Table 5. Results of HZA106827 - Trough FEV_1 (mL) at week 12

Trough FEV_1 (mL) at week 12	Placebo	FF 100 micrograms OD
	(n=193)	(n=203)
Least squares mean	2,525	2,661
Least squares mean change from baseline (SE)	196 (31.0)	332 (30.2)
Comparison against placebo		
Difference	---	136
95% CI	---	51, 222
***P* value**	---	0.002

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

Table 6. Results of HZA106827: 0–24 hour weighted mean FEV_1 (mL) at week 12

0–24 hour weighted mean FEV_1 (mL) at week 12	Placebo	FF 100 micrograms OD
	(n=95)	(n=106)
Least squares mean	2,542	2,728
Least squares mean change from baseline (SE)	212 (45.6)	398 (43.2)
Comparison against placebo		
Difference	---	186
95% CI	---	62, 310
P value	---	0.003

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

FFA11496 was a 24-week study which evaluated the relative efficacy of FF in doses of 100 micrograms and 200 micrograms 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 to 1,000 micrograms/day or equivalent). LABA use was discontinued during the run-in period. The primary efficacy endpoint was change from baseline trough FEV_1 at week 24. The group receiving FF 200 micrograms had generally numerically greater changes from baseline than the group receiving FF 100 micrograms throughout the study. At week 24, the change from baseline in trough FEV_1 was 208 mL for FF 100 micrograms and 284 mL for FF 200 micrograms, a difference of 77 mL, 95% CI: -39, 192).

HZA106829 was a 24-week study and evaluated the efficacy of FF 200 micrograms once daily in the evening, and FP 500 micrograms twice daily on lung function in subjects 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 (fluticasone propionate 500 to 1,000 micrograms/day or equivalent). LABA use was discontinued during the run-in period. Mean baseline percent predicted FEV_1 was approximately 67% in both treatment groups. The trial assessed the non-inferiority of FF 200 micrograms once daily compared with FP 500 micrograms twice daily for trough FEV_1 at week 24. The co-primary endpoint of weighted mean FEV_1 (0-24 hours) was also assessed at the end of the 24-week treatment period. Both FF 200 micrograms once daily and FP 500 micrograms twice daily produced improvements from baseline in lung function. FF 200 micrograms once daily was not inferior to FP 500 micrograms twice daily as assessed by trough FEV_1, as the lower bound of the 95% confidence interval from the treatment difference was greater than the pre-defined non-inferiority margin of -125 mL. Lung function improvements were sustained over 24 hours as seen by change in weighted mean FEV_1.

The results of HZA106829 are shown in Table 7.

Table 7. Results of Study HZA106829

Trough FEV_1 (mL) at week 24	**FF 200 micrograms OD (n=186)**	**FP 500 micrograms BD (n=190)**
Least squares mean	2,358	2,341
Least squares mean change from baseline (SE)	201 (30.3)	183 (30.0)
Comparison against FP 500 BD		
Difference	18	---
95% CI	-66, 102	---

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

0 -24 hour weighted mean FEV_1 (mL) at week 24	**FF 200 micrograms OD (n=83)**	**FP 500 micrograms BD (n=86)**
Least squares mean	2,532	2,462
Least squares mean change from baseline (SE)	328 (49.3)	258 (48.3)

Studies in patients previously treated with non-corticosteroids

FFA109687 was an 8-week study which evaluated the efficacy of a range of doses of FF (25 micrograms – 200 micrograms) on lung function in subjects with asthma compared to placebo. Inhaled FP 100 micrograms twice daily was included as an active control. The

trial included a 4-week run-in during which the subjects were symptomatic while taking their usual non-corticosteroid therapy. The primary endpoint was the change from baseline trough FEV_1 after the 8-week period. The groups receiving FF as once daily doses of 100 micrograms and 200 micrograms had significantly greater changes from baseline in trough FEV_1 than the placebo group. At week 8, the change from baseline trough FEV_1 for FF 100 micrograms once daily was 204 mL greater than placebo, demonstrating that the FF 100 is appropriate for treating patients who are symptomatic on non-corticosteroid therapy.

The results of FF 100 micrograms and 200 micrograms relative to placebo in study FFA109687 are displayed in Table 8.

Table 8. Summary of Data from Study FFA109687

Trough FEV_1 (mL) at week 8	Placebo	FF 100 micrograms OD	FF 200 micrograms OD
	(n=93)	(n=109)	(n=94)
Least squares mean	2,515	2,719	2,745
Least squares mean change from baseline (SE)	137 (42.8)	341 (39.6)	367 (42.8)
Comparison against placebo			
Difference	---	204	230
95% CI	---	89, 319	111, 349
P value	---	<0.001	<0.001

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

Children (aged 5 to less than 12 years)

A 12-week placebo and active controlled trial evaluated the safety and efficacy of fluticasone furoate administered once daily in the evening (25, 50, or 100 micrograms) compared with placebo administered once daily in 593 subjects with asthma aged 5 to less than 12 years. The mean age of subjects was 8 years and mean weight was 32 kilograms. At trial entry, 318 (54%) subjects were taking an inhaled corticosteroid (ICS) and the mean total daily ICS dose was less than or equal to 250 micrograms fluticasone propionate or equivalent. Subjects were symptomatic, had at least a 6-month history of asthma, and had been receiving stable asthma therapy for at least 4 weeks prior to screening. Subjects had to have a pre-bronchodilator peak expiratory flow (PEF) of greater than or equal to 60% to less than or equal to 90% of their best post-bronchodilator value and, in subjects able to perform the manoeuvre, demonstrate a greater than or equal to 12% reversibility of FEV_1 within approximately 10 to 40 minutes following 2 to 4 inhalations of salbutamol inhalation aerosol. The primary endpoint of this trial was the mean change from baseline in daily morning (AM) PEF from the patient electronic daily diary averaged over the 12-week treatment period. The change from baseline in daily AM PEF for all 3 doses of fluticasone furoate was significantly greater than placebo; however, fluticasone furoate 100 micrograms provided no greater benefit than fluticasone furoate 50 micrograms. Change from baseline in PEF is presented in Table 9 below. A secondary endpoint was the change from baseline in the PM trough FEV_1 at week 12, presented in Table 10 below.

Table 9. Results of Study HZA106855 - Least Squares Mean Change from Baseline in PEF (Intent-to-Treat Population)

	Placebo	Fluticasone Furoate 25 micrograms	Fluticasone Furoate 50 micrograms	Fluticasone Furoate 100 micrograms
	(n=119)	(n=118)	(n=120)	(n=118)
Primary endpoint				
AM PEF (L/min)[a]	n=119	n=117	n=118	n=118
LS mean change (SE)	3.3 (2.63)	21.9 (2.66)	22.8 (2.65)	15.8 (2.64)
Difference vs placebo		18.6	19.5	12.5
(95% CI)		(11.3, 26.0)	(12.1, 26.9)	(5.1, 19.8)

[a] *Average over weeks 1 to 12.*
PEF = peak expiratory flow.
LS = least squares.
SE = standard error.
CI = confidence interval.

Table 10. Results of Study HZA106855 - Least Squares Mean Change from Baseline in PM Trough FEV_1 (L) at week 12 (LOCF) (Intent-to-Treat Population)

	Placebo	Fluticasone Furoate 25 micrograms	Fluticasone Furoate 50 micrograms	Fluticasone Furoate 100 micrograms
	(n=119)	(n=118)	(n=120)	(n=118)
Secondary endpoint				
Week 12 (LOCF)				
n	102	96	112	96
LS mean	1.524	1.650	1.545	1.557
LS mean change (SE)	0.128	0.254	0.150	0.162
	(0.0264)	(0.0272)	(0.0252)	(0.0272)
Difference vs placebo		0.126	0.022	0.033
(95% CI)		(0.051, 0.201)	(-0.050, 0.094)	(-0.041, 0.108)

LOCF = Last observation carried forward
LS = least squares.
SE = standard error.
CI = confidence interval.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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 dosing, fluticasone furoate is extensively distributed with an average volume of distribution at steady state of 661 L.

Fluticasone furoate has a low association with red blood cells. In vitro plasma protein binding in human plasma of fluticasone furoate was high, on average >99.6%. There was no decrease in the extent of in vitro plasma protein binding in subjects with renal or hepatic impairment.

Fluticasone furoate is a substrate for P-glycoprotein (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.

Metabolism

Based on in vitro data, the major routes of metabolism of fluticasone furoate in humans are mediated primarily by CYP3A4.

Fluticasone furoate is primarily metabolised through hydrolysis of the S-fluoromethyl carbothioate group to metabolites with significantly reduced corticosteroid activity.

A repeat-dose CYP3A4 drug interaction study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (200/25 micrograms) and the strong CYP3A4 inhibitor ketoconazole (400 milligrams). Co-administration increased mean fluticasone furoate $AUC_{(0-24)}$ and C_{max} by 36% and 33%, respectively. The increase in fluticasone furoate exposure was associated with a 27% reduction in 0-24 h weighted mean serum cortisol.

Excretion

Following oral administration, fluticasone furoate was eliminated in humans mainly by metabolism with metabolites being excreted almost exclusively in faeces. Less than1% of the recovered radioactive dose was eliminated in the urine. The apparent plasma elimination half-life following inhaled administration of fluticasone furoate was, on average, 24 hours.

Special Patient Populations

Population PK meta-analyses for fluticasone furoate were conducted in Phase III studies in subjects with asthma. The impact of demographic covariates (age, gender, weight, BMI, racial group, ethnicity) on the pharmacokinetics of fluticasone furoate were evaluated as part of the population pharmacokinetic analysis.

<u>Race</u>

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.

<u>Children</u>

At steady state, fluticasone furoate systemic exposure following 100 micrograms once daily in children (aged 5 years to less than 12 years) was comparable to systemic

exposure seen following 100 micrograms once daily in adults and adolescents, based on a population PK analysis.

ARNUITY ELLIPTA should not be used in children younger than 5 years of age. The safety and efficacy of fluticasone furoate in children under the age of 5 years have not yet been established.

Elderly

There was no evidence for age (up to 84 years) to affect the pharmacokinetics of fluticasone furoate in subjects with asthma.

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 haemodialysis have not been studied.

Hepatic Impairment

Following repeat dosing of fluticasone furoate/vilanterol 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 (Child-Pugh A, B or C) compared with healthy subjects aged 18 and over. The increase in fluticasone furoate systemic exposure in subjects with moderate hepatic impairment (Child-Pugh B) following repeat-dose administration (fluticasone furoate/vilanterol 200/25 micrograms) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. Dose-normalised fluticasone furoate systemic exposure was similar in subjects with moderate and severe hepatic impairment (Child-Pugh B or C). For patients aged 12 and older with moderate or severe hepatic impairment the maximum daily dose is 100 micrograms.

Gender, Weight and BMI

There was no evidence for gender, weight or Body Mass Index (BMI) to influence the pharmacokinetics of fluticasone furoate based on a population pharmacokinetic analysis of Phase III clinical data.

No dosage adjustment is necessary based on gender, weight or BMI.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fluticasone furoate was not genotoxic in a standard battery of studies.

Carcinogenicity

Fluticasone furoate was not carcinogenic in lifetime inhalation studies in rats or mice at respective doses up to 8.6 and 18.8 micrograms/kilogram/day, yielding systemic

exposures similar to that in patients at the maximum recommended human dose, based on AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate (which contains milk protein). There are 12.5 milligrams of lactose monohydrate per blister.

6.2 INCOMPATIBILITIES

Incompatibilities were not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Following removal from the tray, the product may be stored for a maximum period of one month below 30˚C.

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.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

If stored in a refrigerator, the inhaler should be allowed to return to room temperature for at least one hour before use.

6.5 NATURE AND CONTENTS OF CONTAINER

The plastic Ellipta inhaler consists of a light grey body, a pale orange mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant sachet. The tray is sealed with a peelable foil lid.

The inhaler contains a single strip of 14 or 30 regularly distributed blisters.

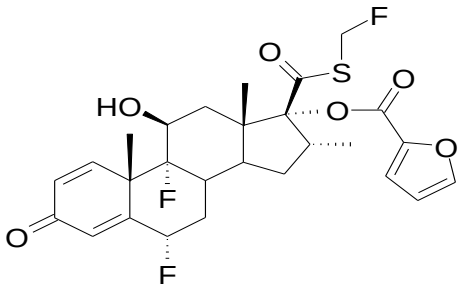
Not all pack sizes may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



The chemical name of fluticasone furoate is androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-, S-(fluoromethyl) ester, (6α,11β,16α,17α)- (9CI).

The molecular formula of fluticasone furoate is $C_{27}H_{29}F_3O_6S$.

Fluticasone furoate is practically insoluble or insoluble in water, and slightly soluble in acetone, dimethylsulphoxide and ethanol.

CAS Number

397864-44-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

GlaxoSmithKline Australia Pty Ltd,
Level 4, 436 Johnston Street,
Abbotsford, Victoria, 3067
Phone: 1800 033 109

www.gsk.com.au

9. DATE OF FIRST APPROVAL

11 September 2015

10. DATE OF REVISION

15 June 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Addition of adverse effects information in post marketing data
All sections	Minor editorial and formatting changes

ARNUITY ELLIPTA was developed in collaboration with Innoviva, Inc.

Version 5.0

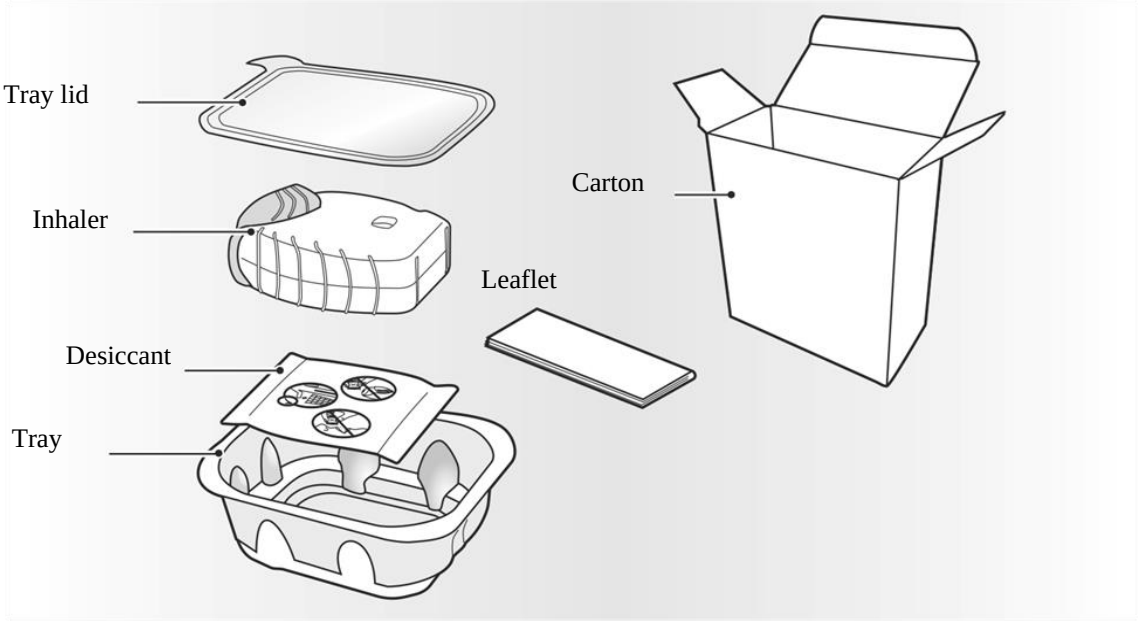
How to Use ARNUITY ELLIPTA

What is the Ellipta inhaler?

ARNUITY ELLIPTA is inhaled through the mouth using the Ellipta inhaler.

When you first use the Ellipta inhaler you do not need to check that it is working properly, and you do not need to prepare it for use in any special way. Just follow these step-by-step instructions.

Your Ellipta inhaler carton contains:



The inhaler is packaged in a tray. **Do not open the tray until you are ready to inhale a dose of your medicine.** When you are ready to use your inhaler, peel back the lid to open the tray. The tray contains a **desiccant** sachet, to reduce moisture. Throw this desiccant sachet away – **do not** open, eat or inhale it.

When you take the inhaler out of the sealed tray, it will be in the ‘closed’ position. **Do not open the inhaler until you are ready to inhale a dose of medicine.** Write the “Discard by” date on the inhaler label in the space provided. The “Discard by” date is one month

from the date you first open the tray. **After this date, the inhaler should no longer be used.**

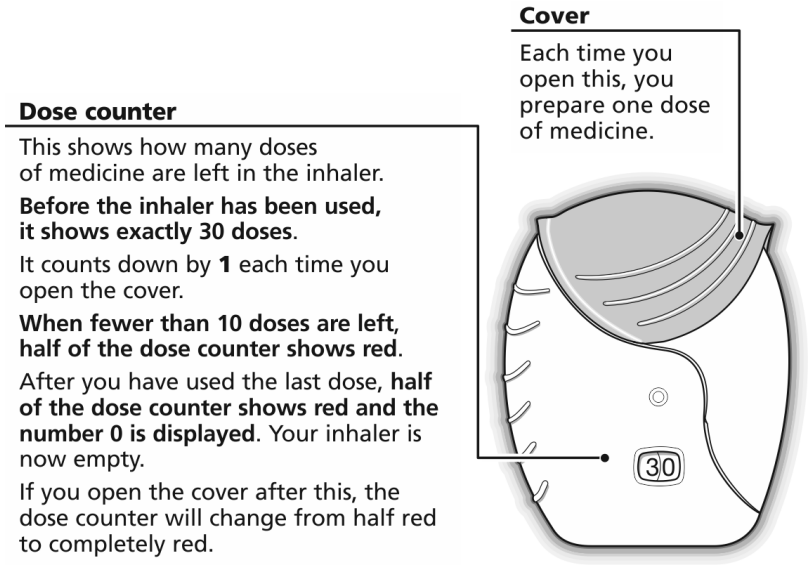
The step-by-step instructions shown below for the 30-dose (30 day supply) Ellipta inhaler also apply to the 14-dose (14 day supply) Ellipta inhaler.

Important information to read 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.

It is not possible to accidentally take extra medicine or a double dose in one inhalation.

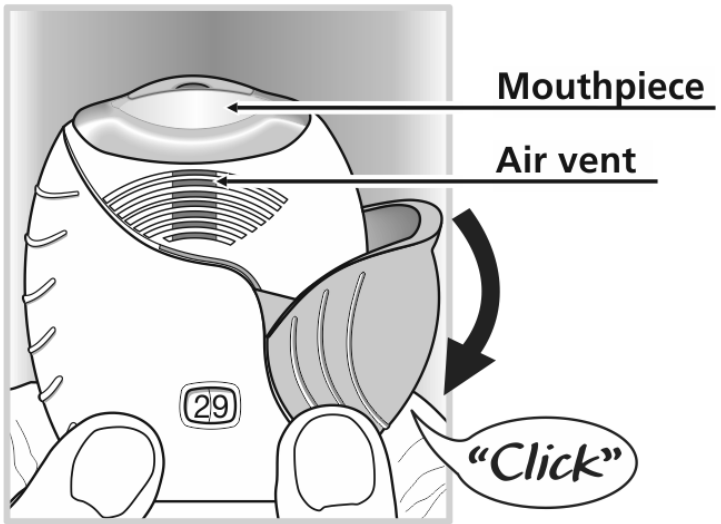


Step 1: Prepare a dose

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

Do not shake the inhaler.

- **Slide the cover down until you hear a "click".**



Your medicine is now ready to be inhaled.

The dose counter counts down by **1** to confirm.

- **If the dose counter does not count down as you hear the "click", the inhaler will not deliver the medicine.**

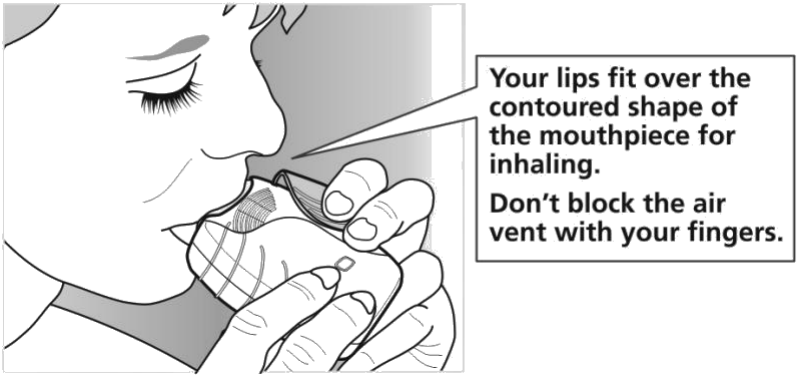
  Take it back to your pharmacist for advice.
- **Do not shake the inhaler at any time.**

Step 2: Inhale your medicine

- **Whilst holding the inhaler away from your mouth, breathe out as far as is comfortable.**

  Do not breathe out into the inhaler.
- **Put the mouthpiece between your lips, and close your lips firmly around it.**

  Do not block the air vent with your fingers.



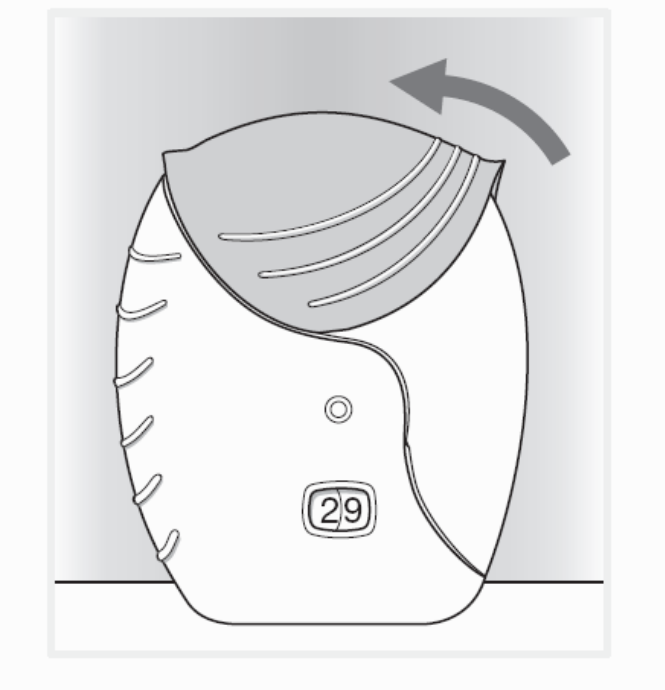
- **Take one long, steady, deep breath in. Hold this breath for about 3-4 seconds or as long as is comfortable.**
- **Remove the inhaler from your mouth.**
- **Breathe out slowly and gently away from the mouthpiece.**

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

If you want to clean the mouthpiece, use a **dry tissue, before** you close the cover.

Step 3: Close the inhaler and rinse your mouth

- **Slide the cover upwards as far as it will go, to cover the mouthpiece.**



- **Rinse your mouth with water without swallowing after you have used the inhaler.**

  This will make it less likely that you will develop a sore mouth or throat as side effects.