INCRUSE ELLIPTA

Version: GDS08/IPI009

INCRUSE ELLIPTA

Umeclidinium

Qualitative and Quantitative Composition

INCRUSE ELLIPTA 62.5 micrograms

Each delivered dose (the dose leaving the mouthpiece of the inhaler) contains 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide). This corresponds to a pre-dispensed dose of 62.5 micrograms of umeclidinium (equivalent to 74.2 micrograms umeclidinium bromide).

Pharmaceutical Form

Inhalation powder, pre-dispensed.

A plastic *ELLIPTA* inhaler consists of a grey body, a light green mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant packet. The tray is sealed with a peelable foil lid.

Clinical Particulars

Indications

INCRUSE ELLIPTA is indicated for maintenance bronchodilator treatment to relieve symptoms associated with chronic obstructive pulmonary disease (COPD).

INCRUSE ELLIPTA in combination with inhaled corticosteroid/long-acting beta2-adrenergic receptor agonists (ICS/LABAs), is indicated for maintenance bronchodilator treatment of chronic obstructive pulmonary disease (COPD). *INCRUSE ELLIPTA* has primarily been studied in combination with *RELVAR* (fluticasone furoate/vilanterol) or *ADVAIR* (fluticasone propionate/salmeterol) (see *Clinical Studies*).

Dosage and Administration

INCRUSE ELLIPTA is for oral inhalation only.

INCRUSE ELLIPTA should be administered once daily at the same time of the day each day.

Adults

The recommended dose is one inhalation of *INCRUSE ELLIPTA* once daily.

Children

Use in patients less than 18 years of age is not relevant given the indication for this product.

Elderly

No dosage adjustment is required in patients over 65 years (see *Pharmacokinetics – Special Patient Populations*).

Renal impairment

No dosage adjustment is required in patients with renal impairment (see *Pharmacokinetics — Special Patient Populations*).

Hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment. *INCRUSE ELLIPTA* has not been studied in patients with severe hepatic impairment (see *Pharmacokinetics — Special Patient Populations*).

Contraindications

INCRUSE ELLIPTA is contraindicated in patients with severe milk-protein allergy.

Warnings and Precautions

INCRUSE ELLIPTA is intended for the maintenance treatment of COPD. It should not be used for the relief of acute symptoms, i.e. as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting bronchodilator. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

As with other inhalation therapies, administration of *INCRUSE ELLIPTA* may produce paradoxical bronchospasm that may be life threatening. Treatment with *INCRUSE ELLIPTA* should be discontinued if paradoxical bronchospasm occurs and alternative therapy instituted if necessary.

Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists, including *INCRUSE ELLIPTA*. Therefore, *INCRUSE ELLIPTA* should be used with caution in patients with severe cardiovascular disorders, especially cardiac arrhythmias.

Consistent with its antimuscarinic activity, *INCRUSE ELLIPTA* should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Interactions

Available clinical data has revealed no clinically relevant drug interactions (see *Clinical Pharmacology*).

Pregnancy and Lactation

Fertility

There are no data on the effects of *INCRUSE ELLIPTA* on human fertility. Animal studies indicate no effects of *INCRUSE ELLIPTA* on fertility (see *Non-clinical information*).

Pregnancy

There is a limited amount of data from the use of *INCRUSE ELLIPTA* in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (See Non-clinical Information).

INCRUSE ELLIPTA should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus.

Lactation

It is unknown whether umeclidinium is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breastfeeding or to discontinue *INCRUSE ELLIPTA* therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *INCRUSE ELLIPTA* on driving performance or the ability to operate machinery. There have been no adverse effects associated with *INCRUSE ELLIPTA* that would affect the ability to perform tasks that require judgement, motor or cognitive skills.

Adverse Reactions

Clinical trial data

The safety profile of umeclidinium was evaluated from approximately 1700 patients with COPD who received doses of 62.5 micrograms or greater for up to one year. This includes approximately 600 patients who received the recommended dose of 62.5 micrograms once daily.

The adverse reactions identified from the four efficacy studies and the long-term safety study (which involved approximately 1400 patients who received umeclidinium) are presented in the table below.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. The following convention has been used for the classification of adverse reactions:

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

MedDRA System organ class	Adverse reaction(s)	Frequency
Infections and infestations	Urinary tract infection Sinusitis Nasopharyngitis Upper Respiratory Tract Infection	Common Common Common Common
Cardiac disorders	Atrial Fibrillation Supraventricular tachycardia Tachycardia	Uncommon Uncommon Common
Respiratory, Thoracic and Mediastinal Disorders	Cough	Common
Gastrointestinal Disorders	Constipation Dry mouth	Uncommon Uncommon

Post-marketing data

MedDRA System organ class	Adverse reaction(s)	Frequency
Immune system disorders	Hypersensitivity reactions including: Rash, urticaria and pruritus Anaphylaxis, angioedema	Uncommon Rare
Nervous system disorders	Dysgeusia	Common

Overdose

No data from clinical studies are available regarding overdose with *INCRUSE ELLIPTA*.

Symptoms and signs

An overdose of *INCRUSE ELLIPTA* will likely produce signs and symptoms consistent with the known inhaled muscarinic antagonist adverse effects (e.g. dry mouth, visual accommodation disturbances and tachycardia).

Treatment

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 national poisons centre, where available.

Pharmacological Properties

Pharmacodynamics

Mechanism of action

Umeclidinium is a long acting muscarinic receptor antagonist (also referred to as an anticholinergic). It is a quinuclidine derivative that is a muscarinic receptor antagonist with activity across multiple muscarinic cholinergic receptor subtypes. Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic cholinergic receptors on airway smooth muscle. It demonstrates slow reversibility at the human M3 muscarinic receptor subtype *in vitro* and a long duration of action *in vivo* when administered directly to the lungs in pre-clinical models.

Pharmacodynamic effects

In a 24-week, placebo controlled clinical efficacy study *INCRUSE ELLIPTA* increased forced expiratory volume in one second (FEV_1) after the first dose on Day 1 with an improvement of 0.07 litres at 15 minutes compared with placebo ($p<0.001$). The increase from baseline to peak FEV_1 over the first 6 hours post-dose at Day 1 was 0.23 litres with *INCRUSE ELLIPTA* compared with 0.11 litres for placebo. The increase from baseline to peak FEV_1 over the first 6 hours post-dose at Week 24 was 0.23 litres with *INCRUSE ELLIPTA* compared with 0.10 litres for placebo.

Cardiovascular effects

The effect of umeclidinium 500 micrograms on the QT interval was evaluated in a placebo- and moxifloxacin-controlled QT trial of 103 healthy volunteers. Following repeat doses of umeclidinium 500 micrograms once daily for 10 days, no clinically relevant effect on prolongation of QT interval (corrected using the Fridericia method) was observed.

Pharmacokinetics

Absorption

Following inhaled administration of umeclidinium in healthy volunteers, C_{max} occurred at 5 to 15 minutes. The absolute bioavailability of inhaled umeclidinium was on average 13% of the dose, with negligible contribution from oral absorption. Following repeat dosing of inhaled umeclidinium, steady state was achieved within 7 to 10 days with 1.5 to 2-fold accumulation. Umeclidinium systemic exposure following inhaled administration was dose proportional.

Distribution

Following intravenous administration to healthy subjects, the mean volume of distribution was 86 litres. *In vitro* plasma protein binding in human plasma was on average 89%.

Metabolism

In vitro studies showed that umeclidinium is principally metabolised by the enzyme P450 CYP2D6 and is a substrate for the P-glycoprotein (Pgp) transporter. The primary metabolic routes for umeclidinium are oxidative (hydroxylation, O-dealkylation) followed by conjugation (glucuronidation, etc), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low.

Drug-drug interactions

Umeclidinium is a substrate of P-glycoprotein transporter (P-gp) and CYP2D6. The effect of the P-gp transporter inhibitor verapamil (240 milligrams once daily) on the steady-state pharmacokinetics of umeclidinium was assessed in healthy volunteers. No effect of verapamil was observed on umeclidinium C_{max}. An approximately 1.4-fold increase in umeclidinium AUC was observed. The effect of lack of CYP2D6 poor metaboliser genotype on the steady-state pharmacokinetics of umeclidinium was assessed in healthy volunteers (CYP2D6 normal metabolisers and CYP2D6 poor metabolisers). No clinically meaningful difference in systemic exposure to umeclidinium (500 micrograms) was observed following repeat daily inhaled dosing to normal and CYP2D6 poor metaboliser subjects.

Elimination

Plasma clearance following intravenous administration was 151 litres/hour. Following intravenous administration, approximately 58% of the administered radiolabelled dose (or 73% of the recovered radioactivity) was excreted in faeces by 192 hours post-dose. Urinary elimination accounted for 22% of the administered radiolabelled dose by 168 hours (27% of recovered radioactivity). The excretion of the drug-related material in the faeces following intravenous dosing indicated secretion into the bile. Following oral administration to healthy male subjects, total radioactivity was excreted primarily in faeces (92% of the administered radiolabelled dose or 99% of the recovered radioactivity) by 168 hours post-dose. Less than 1% of the orally administered dose (1% of recovered radioactivity) was excreted in urine, suggesting negligible absorption following oral administration. Umeclidinium plasma half-life following inhaled dosing for 10 days averaged 19 hours, with 3% to 4% drug excreted unchanged in urine at steady-state.

Special patient populations

Elderly

A population pharmacokinetic analysis showed that pharmacokinetics of umeclidinium are similar between COPD patients 65 years and older and those younger than 65 years of age.

Renal impairment

Subjects with severe renal impairment (creatinine clearance < 30 milliliters/min) showed no evidence of an increase in systemic exposure to umeclidinium (C_{max} and AUC), and no evidence of altered protein binding between subjects with severe renal impairment and healthy volunteers.

Hepatic impairment

Subjects with moderate hepatic impairment (Child-Pugh Class B) showed no evidence of an increase in systemic exposure to umeclidinium (C_{max} and AUC), and no evidence of altered protein binding between subjects with moderate hepatic impairment and healthy volunteers. Umeclidinium has not been evaluated in subjects with severe hepatic impairment.

Other patient characteristics

A population pharmacokinetic analysis showed that no dose adjustment is required for umeclidinium based on the effect of age, race, gender, inhaled corticosteroid use or weight. A study in CYP2D6 poor metabolisers showed no evidence of a clinically significant effect of CYP2D6 genetic polymorphism on systemic exposure to umeclidinium.

Clinical Studies

The efficacy of *INCRUSE ELLIPTA* administered once daily was evaluated in two placebo controlled clinical studies, in adult patients with a clinical diagnosis of COPD; a 12-week study (AC4115408) and a 24-week study (DB2113373).

Placebo Controlled Studies

In the 12-week study, *INCRUSE ELLIPTA* demonstrated statistically significant and clinically meaningful improvements in measures of lung function (as defined by change from baseline trough FEV_1 at Week 12, which was the primary efficacy endpoint compared with placebo (see *Table 1*). The bronchodilatory effects with *INCRUSE ELLIPTA* compared with placebo were evident after the first day of treatment and were maintained over the 12-week treatment period.

Table 1. Primary efficacy endpoint at Week 12 (Study AC4115408)

	Trough FEV_1 (L)		
	Baseline (SD)	Change from baseline (SE)	Difference from Placebo
			Treatment Difference (95% CI) p-value
Study AC4115408			
INCRUSE ELLIPTA 62.5 mcg OD (n= 69)	1.26, (0.57)	0.12, (0.03)	0.13, (0.05, 0.20), <0.001
Placebo (n=68)	1.21, (0.43)	-0.01, (0.03)	-

Abbreviations: CI= confidence interval; FEV_1= forced expiratory volume in 1 second; L= litres; mcg= micrograms; n= number randomized to treatment; OD= once daily; SD= standard deviation; SE= standard error.

INCRUSE ELLIPTA demonstrated a statistically significant greater improvement from baseline in weighted mean FEV_1 over 0-6 hours post-dose at Week 12 compared with placebo (0.17 litres ($p<0.001$)).

The percentage of patients receiving *INCRUSE ELLIPTA* that responded with a minimum clinically important difference (MCID) of ≥1 unit Transition Dyspnoea Index (TDI) focal score at Week 12 was 38% (24/64) compared with 15% (8/53) for placebo. The odds of being a TDI responder vs. a non responder, was statistically significantly greater for *INCRUSE ELLIPTA* compared with placebo at Week 12 (Odds Ratio 3.4 (95% CI 1.3, 8.4), p=0.009).

INCRUSE ELLIPTA demonstrated statistically significant improvements from placebo in the change from baseline in total score at Week 12 for the St. George's Respiratory Questionnaire (SGRQ), a disease-specific health status measure (-7.90 units) ($p<0.001$). The percentage of patients receiving *INCRUSE ELLIPTA* that responded with a reduction of ≥4 units (MCID) in SGRQ total score at Week 12 was 44% (28/63) compared with 26% (14/54) for placebo. The odds of being a SGRQ responder vs. a non responder, was statistically significantly greater for *INCRUSE ELLIPTA* compared with placebo at Week 12 (Odds Ratio 2.44 (95% CI 1.08, 5.50), p=0.032).

In addition, patients treated with *INCRUSE ELLIPTA* required significantly less rescue salbutamol over the 12-week treatment period than those treated with placebo (mean reduction of 0.7 puffs per day and the difference from placebo was statistically significant (p=0.025)).

In the 24-week study, DB2113373, *INCRUSE ELLIPTA* demonstrated statistically significant improvements in lung function (as defined by change from baseline trough FEV_1 at Week 24, which was the primary efficacy endpoint compared with placebo (see *Table 2*). The bronchodilatory effects with *INCRUSE ELLIPTA* compared with placebo were evident after the first day of treatment and were maintained over the 24-week treatment period.

Table 2. Primary efficacy endpoint at Week 24 (Study DB2113373)

	Trough FEV_1 (L)		
	Baseline (SD)	Change from baseline (SE)	Difference from Placebo
			Treatment Difference (95% CI) p-value
Study DB2113373			
INCRUSE ELLIPTA 62.5 mcg OD (n= 418)	1.20 (0.49)	0.12 (0.01)	0.12 (0.08, 0.16) <0.001
Placebo (n=280)	1.20 (0.47)	0.00 (0.02)	-

Abbreviations: CI= confidence interval; FEV_1= forced expiratory volume in 1 second; L= litres; mcg= micrograms; n= number randomized to treatment; OD= once daily; SD= standard deviation; SE= standard error.

INCRUSE ELLIPTA demonstrated a statistically significant greater improvement from baseline in weighted mean FEV_1 over 0-6 hours post-dose at Week 24 compared with placebo (0.15 litres; $p<0.001$).

Statistically significant improvements from placebo in the TDI focal score at Week 24 was demonstrated for *INCRUSE ELLIPTA* (1.0 units) ($p<0.001$) The percentage of patients receiving *INCRUSE ELLIPTA* that responded with a minimum clinically important difference (MCID) of ≥1 unit TDI focal score at Week 24 was 53% (207/394) compared with 41% (106/260) for placebo. The odds of being a TDI responder vs. a non responder, was statistically significantly greater for *INCRUSE ELLIPTA* compared with placebo at Week 24 (Odds Ratio 1.6 (95% CI 1.2, 2.3), p=0.002).

Statistically significant improvements from placebo in the change from baseline in total score at Week 24 for the St. George's Respiratory Questionnaire (SGRQ), a disease-specific health status measure, were also demonstrated for *INCRUSE ELLIPTA* (-4.69 units) ($p\leq0.001$). The percentage of patients receiving *INCRUSE ELLIPTA* that responded with a reduction of ≥4 units (MCID) in SGRQ total score at Week 24 was 44% (172/388) compared with 34% (86/254) for placebo. The odds of being a SGRQ responder vs. a non responder, was statistically significantly greater for *INCRUSE ELLIPTA* compared with placebo at Week 24 (Odds Ratio 1.6 (95% CI 1.2, 2.3), p=0.003).

Treatment with *INCRUSE ELLIPTA* lowered the risk of a COPD exacerbation compared with placebo (analysis of time to first exacerbation; Hazard Ratio 0.6, 95% CI=0.4 to 1.0, risk reduction 40%).

Additional supporting efficacy studies conducted with INCRUSE ELLIPTA in combination with RELVAR (fluticasone furoate/vilanterol) 100/25 micrograms or ADVAIR (fluticasone propionate/salmeterol) 250/50 micrograms in adult patients with a clinical diagnosis of COPD:

In two 12-week, placebo controlled studies (200109 and 200110), the addition of *INCRUSE ELLIPTA* to *RELVAR* (100/25 micrograms) once daily, resulted in statistically significant and clinically meaningful improvements in the primary endpoint of trough FEV_1 at Day 85 compared to placebo plus *RELVAR* (124 mL (95% CI 93, 154, $p<0.001$) and 122 mL (95%CI 91, 152, $p<0.001$)).

In two 12-week, placebo controlled studies (AC4116135 and AC4116136), the addition of *INCRUSE ELLIPTA* to *ADVAIR* (250/50 micrograms) twice daily, resulted in statistically significant and clinically meaningful improvements in the primary endpoint of trough FEV_1 at Day 85 compared to placebo plus *ADVAIR* (147 mL (95% CI 107, 187, $p<0.001$) and 127 mL (95%CI 89, 164, $p<0.001$)).

No new adverse drug reactions were identified with the addition of *INCRUSE ELLIPTA* to *RELVAR* or *ADVAIR* in these studies.

Pre-clinical Safety Data

In non-clinical studies with umeclidinium, findings were those typically associated with the primary pharmacology of muscarinic receptor antagonists and/or local irritancy.

Carcinogenesis/mutagenesis

Umeclidinium was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in mice or rats at exposures ≥ 26 or ≥ 22-fold, times the human clinical exposure of umeclidinium, based on AUC, respectively.

Reproductive Toxicology

Umeclidinium had no adverse effects on male or female fertility in rats.

Umeclidinium was not teratogenic in rats or rabbits. In a pre- and post-natal study, subcutaneous administration of umeclidinium to rats resulted in lower maternal body weight gain and food consumption and slightly decreased pre-weaning pup body weights in dams given 180 micrograms/kg/day dose (approximately 80-times the human clinical exposure of umeclidinium, based on AUC).

Pharmaceutical Particulars

List of Excipients

Lactose monohydrate (which contains milk protein) (12.5 milligrams lactose monohydrate per dose)

Magnesium stearate

Incompatibilities

No incompatibilities have been identified.

Shelf Life

The expiry date is indicated on the packaging.

In-use shelf-life:

Following removal from the tray, the product may be stored for a maximum period of 6 weeks.

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.

Special Precautions for Storage

Do not store above 30°C. If stored in the refrigerator, allow the inhaler to return to room temperature for at least an hour before use.

Nature and Contents of Container

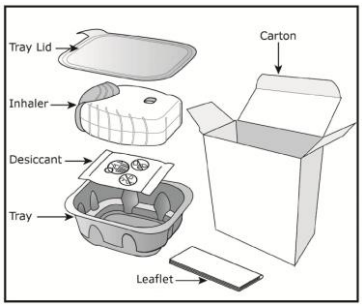
The plastic *ELLIPTA* inhaler consists of a grey body, a light green mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant sachet. The tray is sealed with a peelable foil lid.

The inhaler contains one strip of either 7 or 30 regularly distributed blisters, each containing a white powder.

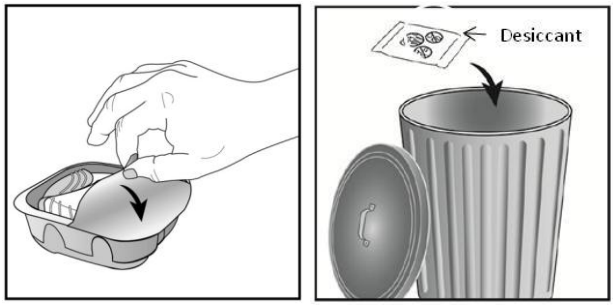
Instructions for Use/Handling

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 the instructions below.

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 **—don't** open, eat or inhale it.

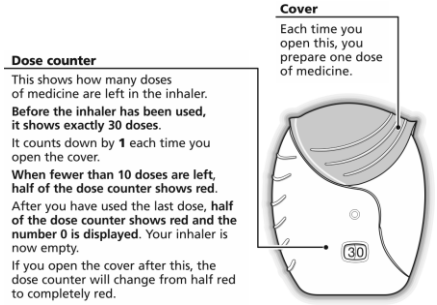


When you take the inhaler out of the sealed tray, it will be in the 'closed' position. **Don't open the inhaler until you are ready to inhale a dose of medicine**. Write the "Discard by" date on the inhaler label in the space provided. The "Discard by" date is 6 weeks from the date you open the tray. **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 7-dose (7 day supply) *ELLIPTA* inhaler.

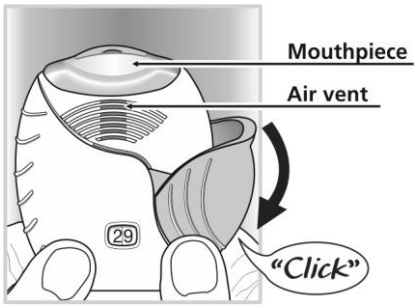
Read this before you start

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



Prepare a dose

- Wait to open the cover until you are ready to take your dose.
- Do not shake the inhaler.
- Slide the cover fully down until you hear a "click".



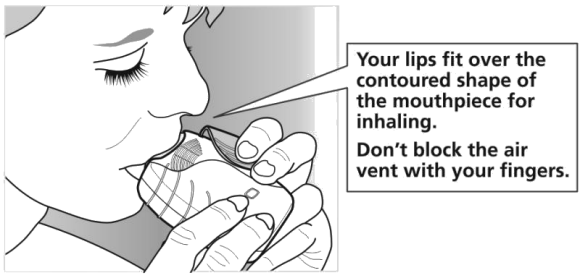
Your medicine is now ready to be inhaled.

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

Inhale your medication

- While holding the inhaler away from your mouth, breathe out as far as is comfortable.
- **Don't** breathe out into the inhaler.
- Put the mouthpiece between your lips, and close your lips firmly around it. **Don't** block the air vent with your fingers.

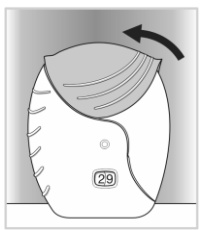


- Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds).
- Remove the inhaler from your mouth.
- Breathe out slowly and gently.

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.

Close the inhaler



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

Not all presentations are available in every country.

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