

















































exposure was not associated with an increase in beta-agonist–related systemic effects on heart rate or blood potassium.

*Cytochrome P450 2D6:* In vitro metabolism of umeclidinium is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to umeclidinium (500 mcg) (8 times the approved dose) was observed following repeat daily inhaled dosing to normal (ultrarapid, extensive, and intermediate metabolizers) and CYP2D6 poor metabolizer subjects.

*Inhibitors of P-glycoprotein:* Fluticasone furoate, umeclidinium, and vilanterol are substrates of P-gp. Coadministration of repeat-dose (240 mg once daily) verapamil (a moderate CYP3A4 inhibitor and a P-gp inhibitor) did not affect the vilanterol  $C_{max}$  or AUC in healthy subjects (Figure 2). Drug interaction trials with a specific P-gp inhibitor and fluticasone furoate have not been conducted. The effect of the moderate P-gp transporter inhibitor verapamil (240 mg once daily) on the steady-state pharmacokinetics of umeclidinium was assessed in healthy subjects. No effect on umeclidinium  $C_{max}$  was observed; however, an approximately 1.4-fold increase in umeclidinium AUC was observed (Figure 3).

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### TRELEGY ELLIPTA

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with TRELEGY ELLIPTA; however, studies are available for the individual components, fluticasone furoate, umeclidinium, and vilanterol, as described below.

#### Fluticasone Furoate

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

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

No evidence of impairment of fertility was observed in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately 8 and 21 times, respectively, the MRHDID for adults on AUC basis).

#### Umeclidinium

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID for adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and at inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID for adults on an AUC basis).

### Vilanterol

In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhaled dose of 29,500 mcg/kg/day (approximately 8,750 times the MRHDID for adults on an AUC basis). No increase in tumors was seen at an inhaled dose of 615 mcg/kg/day (approximately 530 times the MRHDID for adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhaled doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 45 times the MRHDID for adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 2 times the MRHDID for adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay.

No evidence of impairment of fertility was observed in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (both approximately 5,490 times the MRHDID based on AUC).

## **14 CLINICAL STUDIES**

The clinical efficacy of TRELEGY ELLIPTA is based primarily on the coadministration of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg, the components of TRELEGY ELLIPTA, in 2 multicenter, randomized, double-blind, parallel-group, 12-week treatment trials (confirmatory trials). Comparative in vitro data provide support for reliance on coadministration studies with umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg [see Description (11)].

### **14.1 Confirmatory Trials**

The population demographics for Trials 1 and 2 were: mean age of 64 years, 92% white, 66% male, and an average smoking history of 48 pack-years, with 50% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV<sub>1</sub> was 46% (range: 14% to





















**Inactive ingredients:** lactose monohydrate (contains milk proteins), magnesium stearate



For more information about TRELEGY ELLIPTA, call 1-888-825-5249 or visit our website at [www.trelegy.com](http://www.trelegy.com).  
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TRELEGY ELLIPTA was developed in collaboration with Innoviva.

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TRL:xMG

This Medication Guide has been approved by the U.S. Food and Drug Administration

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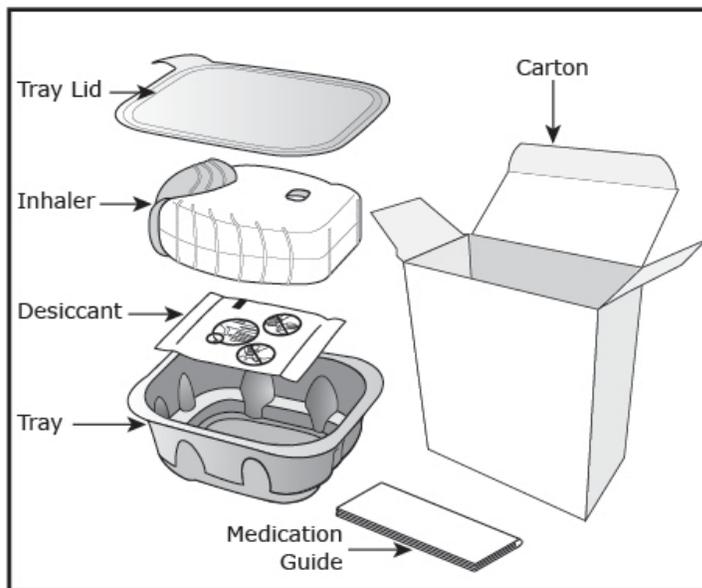
## INSTRUCTIONS FOR USE

### TRELEGY ELLIPTA (TREL-e-gee e-LIP-ta) (fluticasone furoate, umeclidinium, and vilanterol inhalation powder) for oral inhalation

#### Read this before you start:

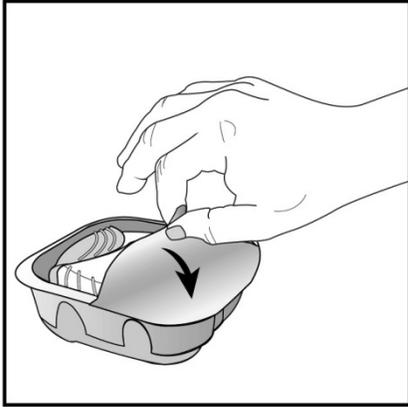
- If you open and close the cover without inhaling the medicine, you will lose the dose.
- The lost dose will be securely held inside the inhaler, but it will no longer be available to be inhaled.
- It is not possible to accidentally take a double dose or an extra dose in 1 inhalation.

#### Your TRELEGY ELLIPTA inhaler

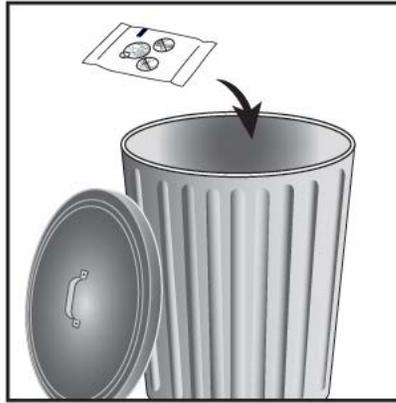


#### How to use your inhaler

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



**Figure A**

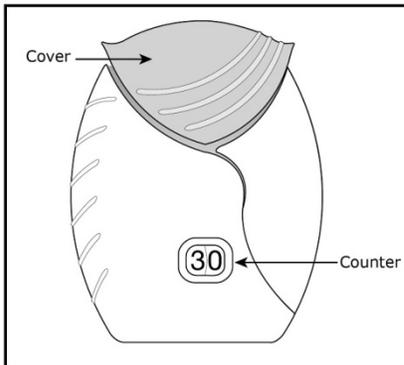


**Figure B**

**Important Notes:**

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

**Check the counter. See Figure C.**

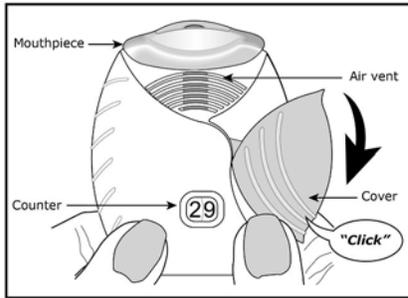


**Figure C**

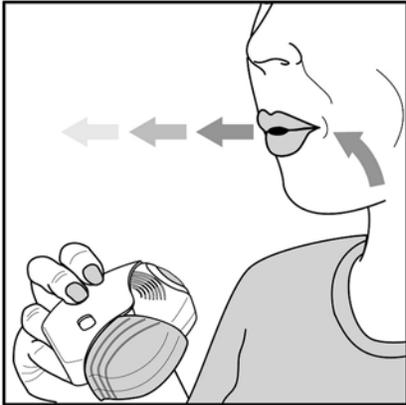
- Before the inhaler is used for the first time, the counter should show the number 30 (14 if you have a sample or institutional pack). This is the number of doses in the inhaler.
- Each time you open the cover, you prepare 1 dose of medicine.
- The counter counts down by 1 each time you open the cover.

**Prepare your dose:**

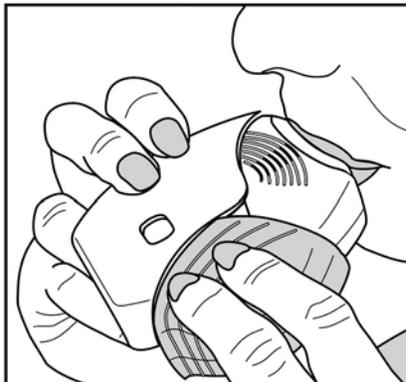
**Wait to open the cover until you are ready to take your dose.**



**Figure D**



**Figure E**



**Figure F**

Do not block the air vent with your fingers.



**Figure G**

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

- Slide the cover down to expose the mouthpiece. You should hear a “click.” The counter will count down by 1 number. You do not need to shake this kind of inhaler.

**Your inhaler is now ready to use.**

- If the counter does not count down as you hear the click, the inhaler will not deliver the medicine. Call your healthcare provider or pharmacist if this happens.

**Step 2. Breathe out. See Figure E.**

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

**Step 3. Inhale your medicine. See Figure F.**

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

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

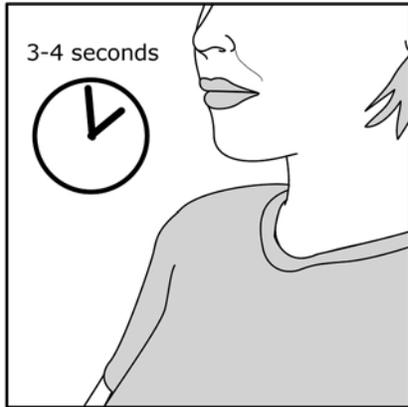


Figure H

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

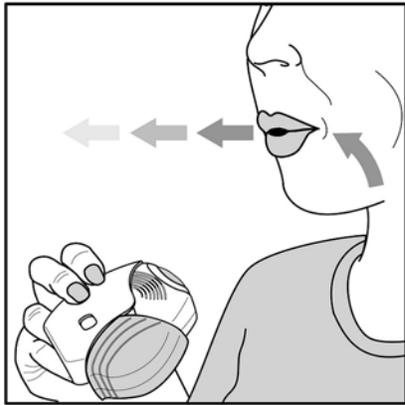


Figure I

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

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

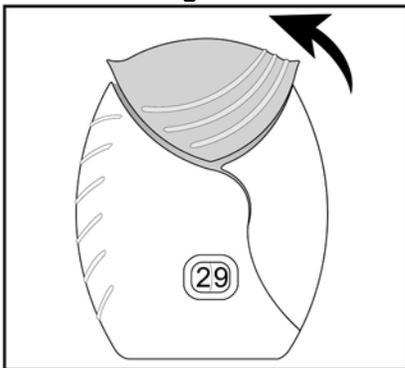


Figure J

**Step 5. Close the inhaler. See Figure J.**

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

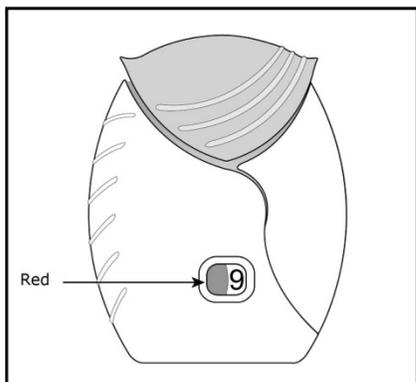


Figure K

**Step 6. Rinse your mouth. See Figure K.**

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

**Important Note: When should you get a refill?**



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

**Figure L**



For more information about TRELEGY ELLIPTA or how to use your inhaler, call 1-888-825-5249 or visit our website at [www.trelegy.com](http://www.trelegy.com).

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TRELEGY ELLIPTA was developed in collaboration with Innoviva.

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