INFORMASI UNTUK PASIEN

RELVAR ELLIPTA
Fluticasone furoate/vilanterol

Penggunaan obat ini tunduk terhadap pengawasan tambahan. Hal ini memungkinkan identifikasi cepat untuk informasi keamanan baru. Anda dapat membantu dengan melaporkan efek samping apapun yang mungkin Anda dapatkan. Lihat *Bagian 4* untuk melaporkan efek samping.

Baca keseluruhan brosur ini secara teliti sebelum Anda mulai menggunakan RELVAR Ellipta karena brosur ini mengandung informasi penting untuk Anda.
- Simpan petunjuk ini. Anda mungkin membutuhkannya untuk dibaca kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat.
- RELVAR Ellipta ini hanya diresepkan kepada Anda. Jangan diberikan kepada orang lain. Hal tersebut dapat membahayakan mereka, meskipun gejala penyakit mereka sama dengan gejala Anda.
- Jika Anda merasakan efek samping, bicarakan dengan dokter, apoteker, atau perawat. Termasuk kemungkinan efek samping lain yang tidak tertulis dalam petunjuk ini. Lihat *Bagian 4*.

Apa saja yang ada dalam petunjuk ini:

1 Apa itu RELVAR Ellipta dan digunakan untuk apa

RELVAR Ellipta mengandung 2 zat aktif yaitu fluticasone furoate dan vilanterol. Terdapat 2 kekuatan RELVAR Ellipta yaitu fluticasone furoate 92 mikrogram/vilanterol 22 mikrogram dan fluticasone furoate 184 mikrogram/vilanterol 22 mikrogram. Kedua kekuatan tersebut disediakan dalam bentuk dosis *pre-dispensed* 100/25 mikrogram dan 200/25 mikrogram dari fluticasone furoate/vilanterol (trifenatate).

Dosis 100/25 mikrogram digunakan untuk terapi reguler Penyakit Paru Obstruktif Kronis (**PPOK**) pada pasien dewasa, dan **asma** pada pasien dewasa serta anak usia 12 tahun ke atas.

Dosis 200/25 mikrogram digunakan untuk terapi **asma** pada pasien dewasa serta anak usia 12 tahun ke atas.

Gunakan RELVAR Ellipta secara teratur setiap hari dan jangan hanya saat Anda mengalami gangguan pernapasan atau gejala PPOK dan asma lainnya. RELVAR Ellipta tidak digunakan untuk mengatasi serangan mendadak dari sesak napas atau mengi. Jika Anda terkena serangan ini, Anda harus segera menggunakan inhaler pelega kerja cepat (seperti salbutamol).

Fluticasone furoate masuk ke dalam golongan obat kortikosteroid, biasa disebut steroid. Kortikosteroid mengurangi peradangan. Obat tersebut mengurangi pembengkakan dan iritasi saluran pernapasan kecil pada paru-paru dan mengatasi gangguan pernapasan secara bertahap. Kortikosteroid juga membantu mencegah serangan asma dan memburuknya PPOK.

Vilanterol masuk ke dalam golongan obat bronkodilator kerja panjang. Obat ini merelaksasi otot saluran pernapasan kecil pada paru-paru. Obat ini membantu membuka saluran udara dan mempermudah keluar masuknya udara dalam paru-paru. Jika digunakan secara teratur, obat ini akan membantu saluran pernapasan kecil tersebut tetap terbuka.

Jika Anda menggunakan 2 zat aktif tersebut bersama-sama secara teratur, akan membantu mengontrol kesulitan bernapas Anda dengan lebih baik dibandingkan dengan menggunakannya secara terpisah.

Asma merupakan penyakit serius, penyakit jangka panjang paru-paru dimana otot di sekitar saluran udara terkecil menjadi kencang (bronkokonstriksi) serta membengkak dan iritasi (inflamasi). Gejala datang dan pergi, termasuk sesak napas, mengi, dada tertekan, dan batuk.

Penyakit Paru Obstruktif Kronis (PPOK) juga merupakan penyakit serius, penyakit jangka panjang paru-paru dimana saluran udara meradang dan menebal. Gejala termasuk sesak napas, mengi, dada terasa tidak nyaman, dan batuk berdahak. RELVAR Ellipta ditunjukkan dapat mengurangi munculnya

gejala PPOK.

2 Apa yang perlu Anda ketahui sebelum menggunakan RELVAR Ellipta

Jangan gunakan RELVAR Ellipta:
Jika Anda **alergi** terhadap fluticasone furoate, vilanterol, atau bahan lain dari RELVAR Ellipta *(terdaftar di Bagian 6).*

Jika Anda merasa hal tersebut di atas berlaku untuk Anda, **jangan gunakan** RELVAR Ellipta hingga Anda berkonsultasi ke dokter.

Perhatian dan Pencegahan
Bicarakan dengan dokter Anda sebelum menggunakan RELVAR Ellipta:
- Jika Anda memiliki **penyakit hati**, dapat membuat Anda lebih mungkin terkena efek samping. Jika Anda memiliki penyakit hati sedang atau parah, dokter Anda akan membatasi dosis Anda ke dosis Relvar Ellipta terendah (100/25 mikrogram satu kali sehari).
- Jika Anda memiliki **gangguan jantung** atau **tekanan darah tinggi**.
- Jika Anda memiliki tuberculosis (TB) pada paru-paru, atau infeksi yang berlangsung lama maupun tak terobati.
- Jika Anda memiliki riwayat diabetes.
- Jika Anda memiliki **masalah kelenjar tiroid**.
- Jika Anda memiliki kadar **kalium yang rendah** dalam darah.
- Jika Anda mengalami pandangan kabur atau gangguan penglihatan.

Pastikan dengan dokter jika Anda merasa hal tersebut di atas berlaku terhadap Anda.

Kesulitan Bernapas Mendadak
Jika pernapasan atau mengi Anda memburuk tepat setelah menggunakan RELVAR Ellipta, **hentikan penggunaan** dan segera **cari pertolongan medis**.

Infeksi Paru-Paru
Jika Anda menggunakan RELVAR Ellipta untuk terapi PPOK, Anda memiliki resiko yang lebih tinggi untuk mengalami infeksi paru-paru yang dikenal sebagai pneumonia. Lihat Bagian 4 ‘Efek samping yang mungkin terjadi’ untuk informasi gejala yang perlu diperhatikan ketika menggunakan obat ini. Segera beritahukan dokter jika timbul salah satu gejala tersebut.

Anak-Anak dan Remaja
RELVAR Ellipta tidak direkomendasikan untuk anak-anak usia di bawah 12 tahun untuk terapi asma, atau pada anak-anak dan remaja usia berapapun untuk terapi PPOK.
Obat Lain dan RELVAR Ellipta
Beritahukan dokter atau apoteker jika Anda sedang, baru saja, atau akan menggunakan obat lain, termasuk obat yang didapat tanpa resep dokter.

Beberapa obat dapat mempengaruhi cara kerja RELVAR Ellipta, atau membuat Anda memiliki resiko lebih tinggi untuk mengalami efek samping. Obat tersebut meliputi:
- Obat beta bloker, seperti Metoprolol, untuk terapi **tekanan darah tinggi** atau **gangguan jantung** lainnya
- Ketokonazole, untuk terapi **infeksi yang disebabkan jamur**
- Ritonavir atau Cobicistat, untuk terapi **infeksi HIV**
- β_2-adrenergik agonis kerja panjang (LABA), seperti Salmeterol

Beritahukan dokter atau apoteker jika Anda sedang menggunakan obat-obatan di atas. Dokter akan mengawasi jika Anda sedang menggunakan obat-obatan di atas karena dapat meningkatkan efek samping RELVAR Ellipta.

Kehamilan
RELVAR Ellipta hanya dipertimbangkan untuk diberikan kepada ibu hamil jika manfaat lebih besar daripada resiko.
Jika Anda hamil, merasa mungkin hamil, atau berencana untuk memiliki anak, tanyakan saran ke dokter Anda sebelum menggunakan RELVAR Ellipta.

Ibu Menyusui
Tidak diketahui apakah bahan-bahan RELVAR Elipta dapat melalui ASI. Oleh karena itu, resiko terhadap bayi yang menyusu tidak dapat dikesampingkan.

Jika Anda sedang menyusui, tanyakan saran ke dokter Anda sebelum menggunakan RELVAR Ellipta.

Berkendara dan Menjalankan Mesin
RELVAR Ellipta cenderung tidak mempengaruhi kemampuan Anda mengemudi atau menjalankan mesin.

RELVAR Ellipta Mengandung Laktosa
Jika Anda sudah diberitahu oleh dokter bahwa Anda intoleran terhadap gula atau protein susu, hubungi dokter Anda sebelum menggunakan RELVAR Ellipta.

3 Bagaimana menggunakan RELVAR Ellipta

Selalu gunakan obat sesuai petunjuk dokter. Pastikan dengan dokter atau apoteker apabila Anda tidak yakin.

Seberapa Banyak Obat Digunakan
Asma
Dosis yang direkomendasikan untuk terapi asma adalah satu kali hirupan dosis 100/25 mikrogram satu kali sehari pada waktu yang sama.
Jika Anda memiliki asma parah, dokter mungkin akan memutuskan bahwa Anda harus menggunakan satu kali hirupan dosis yang lebih tinggi yaitu dosis 200/25 mikrogram. Dosis ini juga digunakan satu kali sehari pada waktu yang sama.

PPOK
Dosis yang direkomendasikan untuk terapi PPOK adalah satu kali hirupan 100/25 mikrogram satu kali sehari pada waktu yang sama.

Dosis RELVAR Ellipta yang lebih tinggi tidak cocok untuk terapi PPOK. Pada terapi PPOK, tidak terdapat manfaat tambahan dari penggunaan dosis 200/25 mikrogram dibandingkan dengan dosis 100/25 mikrogram dan terdapat potensi meningkatnya risiko pneumonia serta kejadian tidak diinginkan yang berhubungan dengan kortikosteroid sistemik.

Gunakan Relvar Ellipta pada waktu yang sama setiap hari karena obat efektif selama 24 jam
Sangat penting untuk Anda menggunakan RELVAR Ellipta setiap hari, seperti yang dianjurkan oleh dokter. Hal ini akan membantu Anda bebas dari munculnya gejala selama sehari semalam.

RELVAR Ellipta tidak digunakan untuk mengatasi serangan mendadak dari sesak napas atau mengi. Jika Anda terkena serangan ini, Anda harus segera menggunakan inhaler pelega kerja cepat (seperti salbutamol).

Jika Anda menjadi lebih sering merasakan susah bernapas atau mengi, atau jika Anda menggunakan inhaler pelega kerja cepat lebih banyak daripada biasanya, hubungi dokter.

Bagaimana Cara Menggunakan Inhaler Ellipta
Lihat *Bagian 7* dalam brosur ini untuk informasi lengkapnya.
Anda tidak membutuhkan persiapan RELVAR Ellipta secara khusus, bahkan untuk penggunaan pertama kali.

Jika Gejala Anda Tidak Membaik
Jika gejala Anda (sesak napas, mengi, batuk) tidak membaik atau menjadi semakin memburuk, atau jika Anda juga sedang menggunakan inhaler aksi cepat lebih sering:
Hubungi dokter Anda secepat mungkin

Jika Anda Menggunakan RELVAR Ellipta Lebih dari yang Seharusnya
Jika Anda secara tidak sengaja menggunakan RELVAR Ellipta lebih banyak, segera hubungi dokter atau apoteker. Anda mungkin merasakan bahwa jantung Anda berdetak lebih cepat dari biasanya, tubuh Anda gemetar, atau sakit kepala.

Jika Anda telah menggunakan lebih dari yang dianjurkan dalam waktu yang lama, sangat penting untuk Anda meminta saran kepada dokter atau apoteker. Hal ini dikarenakan dosis yang lebih besar dari RELVAR Ellipta dapat mengurangi jumlah hormon steroid yang secara alami diproduksi oleh tubuh.

Jika Anda Lupa untuk Menggunakan RELVAR Ellipta
Jangan menggunakan dosis tambahan untuk mengganti dosis yang terlewatkan. Cukup gunakan

dosis selanjutnya di waktu yang sama.

Jika Anda menjadi mengi atau sesak napas, atau mulai muncul gejala serangan asma, **gunakan inhaler aksi cepat Anda** (seperti salbutamol), kemudian carilah saran medis.

Jangan Menghentikan Penggunaan RELVAR Ellipta Tanpa Saran Dokter
Gunakan RELVAR Ellipta sesuai dengan jangka waktu yang direkomendasikan dokter. RELVAR Ellipta hanya akan efektif selama Anda menggunakannya. Jangan menghentikan penggunaan kecuali disarankan oleh dokter, bahkan meski Anda merasa sehat.

Jika Anda memiliki pertanyaan lebih jauh pada penggunaan obat ini, tanyakan dokter, apoteker, atau perawat.

4 Efek samping yang mungkin terjadi

Seperti obat lainnya, obat ini dapat menyebabkan efek samping, meski tidak semua pasien mengalaminya.

Reaksi Alergi
Jarang terjadi reaksi alergi terhadap RELVAR Ellipta (terjadi kurang dari 1 dalam 1.000 pasien).

Jika Anda merasakan gejala di bawah ini setelah menggunakan RELVAR Ellipta, **hentikan penggunaan dan segera hubungi dokter.**
- Ruam pada kulit (gatal dan bintik-bintik) atau kemerahan
- Bengkak, kadang pada wajah atau mulut (angioedema)
- Mengi bertambah parah, batuk, atau kesulitan bernapas
- Mendadak merasa lemah atau kepala terasa ringan (yang dapat mengakibatkan roboh atau hilang kesadaran)

Jarang terjadi kesulitan benapas mendadak setelah menggunakan RELVAR Ellipta (terjadi kurang dari 1 dalam 1.000 pasien).

Kesulitan Bernapas Mendadak
Jika napas atau mengi Anda memburuk tepat setelah menggunakan RELVAR Ellipta, **hentikan penggunaan** dan **segera cari bantuan medis**.

Pneumonia (Infeksi Paru-Paru) (efek samping yang umum terjadi)

Beritahukan dokter jika Anda mengalami gejala berikut saat menggunakan RELVAR Ellipta, dimana dapat menjadi gejala dari infeksi paru-paru:
- Demam atau meriang
- Produksi dahak meningkat, perubahan warna dahak
- Batuk meningkat atau meningkatnya kesulitan bernapas

Efek samping lain:
Efek Samping yang Sangat Umum Terjadi
Hal ini mungkin dapat terjadi pada **≥1/10** pasien:
- Sakit kepala
- Nasofaringitis

Efek Samping yang Umum Terjadi
Hal ini mungkin dapat terjadi pada **≥1/100** dan **<1/10** pasien:
- Infeksi saluran pernapasan atas
- Bronkitis
- Influenza
- Kandidiasis pada mulut dan tenggorokan
- Nyeri orofaringeal
- Sinusitis
- Faringitis
- Rhinitis
- Batuk
- Suara serak
- Nyeri pada bagian perut
- Nyeri sendi
- Nyeri punggung

- Demam
- Kejang otot

Efek Samping yang Tidak Umum Terjadi
Hal ini mungkin dapat terjadi pada **≥1/1.000** dan **≤1/100** pasien:
- Denyut jantung yang tidak teratur
- Pandangan kabur

Efek Samping yang Jarang Terjadi
Hal ini mungkin dapat terjadi pada **≥1/10.000** dan **<1/1.000** pasien:
- Reaksi hipersensitif termasuk anafilaksis, angioedema, ruam, dan urtikaria
- Gangguan kecemasan
- Tremor
- Palpitasi
- Takikardi
- Bronkospasme paradoksal

Pelaporan Efek Samping
Jika Anda merasakan efek samping, laporkan ke dokter, apoteker, atau perawat. Termasuk kemungkinan efek samping lain yang tidak tertulis dalam brosur ini.
Laporkan Kejadian Tidak Diinginkan (KTD) ke GSK Indonesia melalui situs web https://gsk.public.reportum.com

5 Bagaimana cara penyimpanan RELVAR Ellipta

Simpan obat ini jauh dari jangkauan anak-anak.

Jangan menggunakan obat setelah tanggal kadaluwarsa, yang ditulis pada label dan karton setelah kata 'EXP'. Tanggal kadaluwarsa merujuk pada hari terakhir bulan tersebut.
Simpan di bawah suhu 30ºC.

Simpan kemasan supaya terjaga dari kelembaban dan jangan membuka *foil* penutup hingga siap untuk penggunaan pertama. Setelah *foil* penutup terbuka, inhaler Ellipta dapat digunakan hingga 1 bulan ke depan, dimulai dari tanggal pembukaan bungkus kemasan. Tulis tanggal kapan inhaler Ellipta harus dimusnahkan pada bagian label inhaler yang tersedia. Tanggal harus ditambahkan segera setelah inhaler dibuka dari bungkus kemasannya.

Jika Anda menyimpan dalam lemari es, **biarkan inhaler Ellipta kembali ke suhu ruangan minimal satu jam** sebelum penggunaan.

Jangan membuang obat apapun di air limbah atau limbah rumah tangga. Tanyakan pada apoteker bagaimana membuang obat yang tidak digunakan lagi. Langkah ini membantu dalam menjaga lingkungan.

6 Isi dari kemasan dan informasi lain

Kandungan Relvar Ellipta
Zat aktif RELVAR Ellipta adalah fluticasone furoate dan vilanterol. Setiap satu hirupan memberikan dosis terlepas (dosis yang meninggalkan *mouthpiece*) sebanyak 92 atau 184 mikrogram fluticasone furoate dan 22 mikrogram vilanterol (dalam bentuk trifenatate).

Dosis di atas setara dengan dosis *pre-dispensed* 100 atau 200 mikrogram fluticasone furoate dan 25 mikrogram vilanterol (dalam bentuk trifenatate).

Bahan lainnya adalah Lactose monohydrate dan Magnesium stearate.

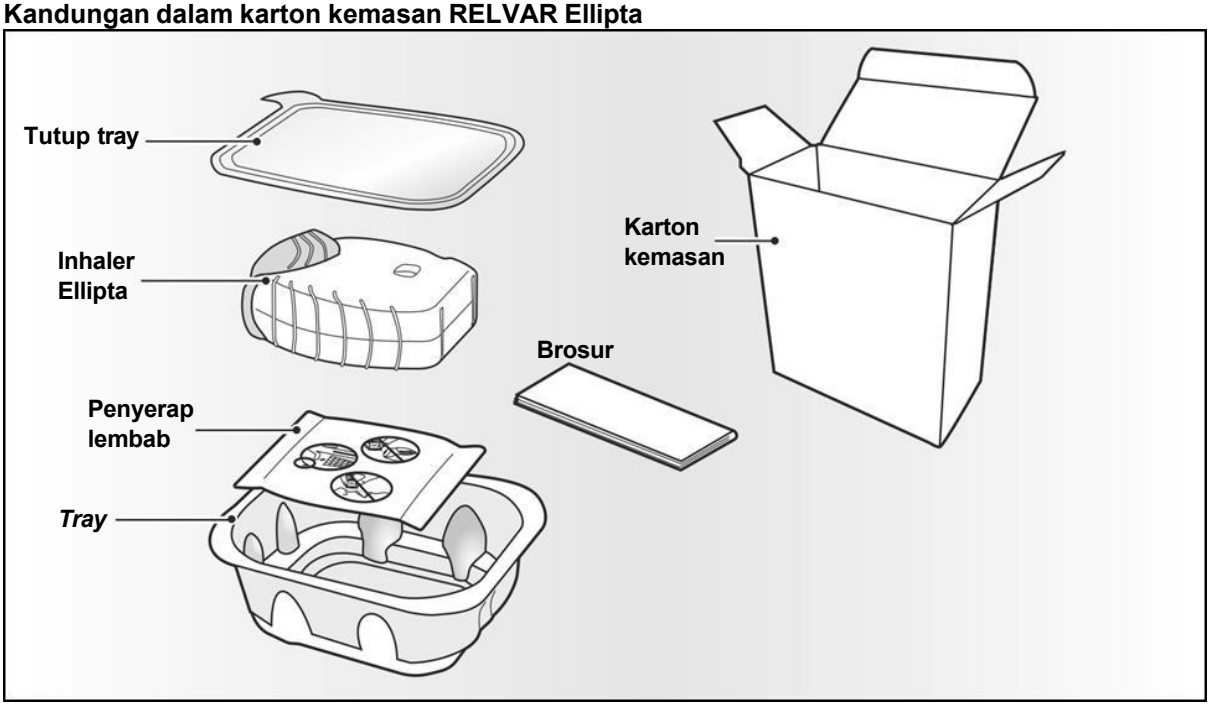
Seperti Apa Bentuk RELVAR Ellipta dan Isi dari Kemasan
Inhaler Ellipta sendiri terdiri dari komponen plastik abu-abu, tutup *mouthpiece* berwarna biru muda, dan penghitung dosis. RELVAR Ellipta dikemas dalam *tray* terlaminasi *foil* dengan tutup *foil* yang mudah dikelupas. Di dalam *tray* terdapat penyerap lembab untuk mengurangi kelembaban di dalam kemasan. Ketika Anda telah membuka tutup *tray*, buanglah bungkus penyerap lembab, jangan dibuka, dimakan atau dihirup. Inhaler Ellipta tidak perlu disimpan di dalam *tray* terlaminasi *foil* ketika sudah dibuka.
Tiap inhaler mengandung 30 dosis.

7 Cara Pakai

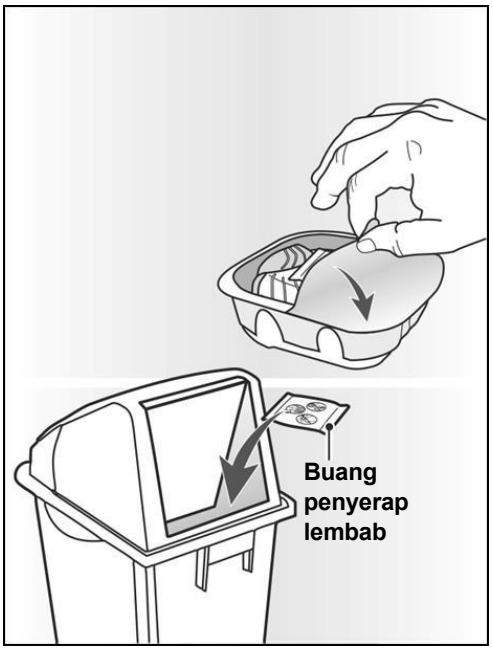
Apa itu inhaler Ellipta?

Saat pertama kali Anda menggunakan RELVAR Ellipta, Anda tidak perlu mencoba apakah inhaler Ellipta bekerja dengan baik, dan Anda tidak membutuhkan persiapan RELVAR Ellipta secara khusus. Cukup ikuti cara pakai berikut.

Kandungan dalam karton kemasan RELVAR Ellipta



Inhaler dikemas dalam *tray.* **Jangan membukanya hingga Anda siap untuk menghirup dosis obat**. Saat Anda siap untuk menggunakan inhaler Ellipta, kupas tutup *tray*. *Tray* mengandung sebungkus penyerap lembab untuk untuk mengurangi kelembaban. Buanglah bungkus penyerap lembab tersebut, **jangan** dibuka, dimakan, atau dihirup.



Ketika Anda mengambil inhaler Ellipta keluar dari kemasannya, inhaler Ellipta akan dalam keadaan ‘tertutup’. **Jangan membukanya hingga Anda siap untuk menghirup dosis obat**. Ketika *tray* dibuka, tulis tanggal ‘Pemusnahan’ pada bagian label inhaler yang tersedia. Tanggal ‘Pemusnahan’ adalah 1 bulan dari tanggal *tray* dibuka. Setelah tanggal ‘Pemusnahan’ tersebut sebaiknya inhaler Ellipta tidak digunakan lagi. *Tray* dapat dimusnahkan setelah dibuka pertama kali.

1) Baca Langkah Berikut Sebelum Anda Memulai

Jika Anda membuka dan menutup tutup tanpa menghirup obat, Anda akan kehilangan dosis. Dosis yang hilang akan aman tertahan di dalam inhaler, namun tidak lagi tersedia.

Tidak memungkinkan untuk secara tidak sengaja menggunakan kelebihan dosis atau dosis ganda dalam satu hirupan.

Penghitung dosis

Penghitung dosis menunjukkan berapa dosis yang masih tersisa di dalam inhaler Ellipta.

Sebelum inhaler Ellipta digunakan, penghitung akan menunjukkan tepat 30 dosis.

Penghitung ini akan menghitung mundur **1** angka setiap Anda membuka tutup.

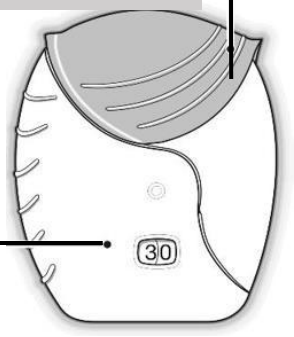
Saat dosis tersisa kurang dari 10, separuh penghitung dosis akan berwarna merah.

Setelah Anda menggunakan dosis terakhir, **separuh penghitung dosis akan berwarna merah dan angka 0 akan ditunjukkan.** Inhaler Ellipta kosong.

Jika Anda membuka tutup setelahnya, penghitung dosis akan berubah menjadi merah semua.

Tutup

Setiap Anda membukanya, Anda menyiapkan 1 dosis obat

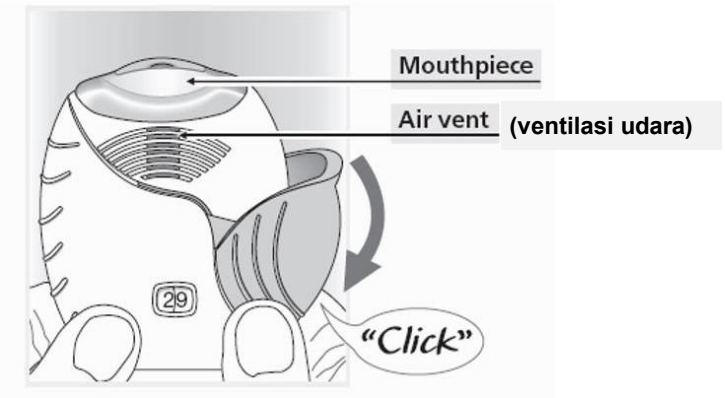


2) Menyiapkan dosis

Buka tutup saat Anda sudah siap menggunakan dosis Anda.

Jangan kocok Inhaler Ellipta.

- Geser tutup ke bawah hingga terdengar bunyi ‘klik’.



Sekarang, obat Anda siap untuk dihirup.

Penghitung dosis berkurang **1** untuk memastikannya.

- **Jika penghitung dosis Anda tidak berkurang ketika terdengar bunyi ‘klik’, inhaler Ellipta tidak akan menghantarkan obat.**
  Kembalikan produk obat ini ke Apoteker untuk meminta saran.

3) Hirup obat Anda

- Saat Inhaler Anda pegang jauh dari mulut, hembuskan napas sebanyak dan senyaman Anda. **Jangan** hembuskan napas ke dalam inhaler.
- **Letakkan *mouthpiece* di antara bibir Anda, dan tutup rapat menyelubungi *mouthpiece.***
  Jangan tutup ventilasi udara dengan jari Anda.

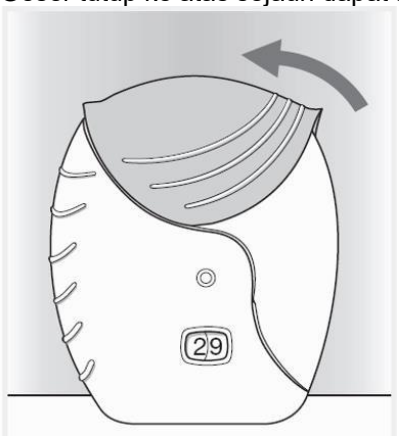
- Tarik napas kuat dan panjang melalui mulut. Tahan napas tersebut selama Anda mampu (minimal 3-4 detik).
- Lepas inhaler Ellipta dari mulut Anda.
- Hembuskan napas perlahan.

Kemungkinan Anda tidak dapat merasakan obatnya, meski Anda menggunakan inhaler dengan benar.

Jika Anda ingin membersihkan *mouthpiece,* gunakan **tisu kering** sebelum menutupnya.

4) Penutupan Inhaler Ellipta dan Berkumur

- Geser tutup ke atas sejauh dapat tergeser untuk menutup *mouthpiece*.



- **Berkumurlah dengan air untuk membasuh mulut Anda setelah menggunakan inhaler, jangan ditelan**
  Dengan demikian kemungkinan kecil Anda akan mengalami nyeri saat menelan sebagai efek samping.

HARUS DENGAN RESEP DOKTER

RELVAR ELLIPTA 100/25 mikrogram, Dus, 1 inhaler Ellipta @ 30 dosis Reg. No. DKI1875705067A1
RELVAR ELLIPTA 200/25 mikrogram, Dus, 1 inhaler Ellipta @ 30 dosis Reg. No. DKI1875705067B1

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Reference : first approvable letter (10 Dec 2018) + redactional change on manufacturer (to align with GMP details, local labelling change)
Date of local revision : 19 Dec 2025

RELVAR ELLIPTA
Fluticasone furoate/Vilanterol

1. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each pre-dispensed dose contains either 100/25 micrograms or 200/25 micrograms of Fluticasone furoate/Vilanterol (as trifenatate).

Each single inhalation of Fluticasone furoate/Vilanterol provides a delivered dose of 92/22 micrograms of Fluticasone furoate/Vilanterol or 184/22 micrograms of Fluticasone furoate/Vilanterol.

Excipients with known effect:
Each delivered dose contains approximately 25 mg of Lactose (as monohydrate). For the full list of excipients, see section 5.1.

2. PHARMACEUTICAL FORM
Inhalation powder

3. CLINICAL PARTICULARS
3.1 Indications ASTHMA
RELVAR ELLIPTA is indicated for the maintenance treatment of asthma.

COPD
RELVAR ELLIPTA is indicated for the maintenance bronchodilator treatment to relieve symptoms associated with chronic obstructive pulmonary disease (COPD) in patients with an exacerbation history.

3.2 Dosage and Administration
RELVAR ELLIPTA is for inhalation only.

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

After inhalation, the patient should rinse their mouth with water without swallowing.

ASTHMA
Patients should be made aware that *RELVAR ELLIPTA* must be used regularly, even when asymptomatic.

If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

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

Populations
Adults and adolescents aged 12 years and over
The recommended dose of *RELVAR ELLIPTA* is:

One inhalation of *RELVAR ELLIPTA* 100/25 micrograms once daily.

or

One inhalation of *RELVAR ELLIPTA* 200/25 micrograms once daily.

A starting dose of *RELVAR ELLIPTA* 100/25 micrograms should be considered for patients who require a low to mid dose of inhaled corticosteroid in combination with a long acting beta$_2$-agonist.

RELVAR ELLIPTA 200/25 micrograms should be considered for patients who require a higher dose of inhaled corticosteroid in combination with a long acting beta$_2$-agonist.

If patients are inadequately controlled on *RELVAR ELLIPTA* 100/25 micrograms, consider increasing the dose to 200/25 micrograms, which may provide additional improvement in asthma control.

Children
The safety and efficacy of *RELVAR ELLIPTA* has not been established in children less than 12 years of age.

COPD
Populations Adults
The recommended dose of *RELVAR ELLIPTA* is:

One inhalation of *RELVAR ELLIPTA* 100/25 micrograms once daily.

RELVAR ELLIPTA 200/25 micrograms is not indicated for patients with COPD. There is no additional benefit of the 200/25 micrograms dose compared to the 100/25 micrograms dose and there is a potential increased risk of pneumonia and systemic corticosteroid-related adverse reactions.

Children
The use in children is not relevant given the COPD indication for this product.

Special population: Asthma and COPD
Elderly
No dosage adjustment is required in patients over 65 years (see *Pharmacokinetics – Special Patient Populations*).

Renal impairment
No dose adjustment is required for patients with renal impairment (see *Pharmacokinetics*).

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 (AUC) (see *Pharmacokinetics*).

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 with moderate or severe hepatic impairment the maximum dose is 100/25 micrograms (see *Pharmacokinetics*).

3.3 Contraindications
RELVAR ELLIPTA is contraindicated in patients with severe milk-protein allergy or who have demonstrated hypersensitivity to either Fluticasone furoate, Vilanterol or any of the excipients.

3.4 Warnings and Precautions Exacerbations
RELVAR ELLIPTA should not be used to treat acute asthma symptoms or an acute exacerbation in COPD, for which a short-acting bronchodilator is required. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

Patients should not stop therapy with *RELVAR ELLIPTA*, in asthma or COPD, without physician supervision since symptoms may recur after discontinuation.

Asthma-related adverse events and exacerbations may occur during treatment with *RELVAR ELLIPTA*. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of *RELVAR ELLIPTA*.

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. *RELVAR ELLIPTA* should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Cardiovascular effects
Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic drugs, including *RELVAR ELLIPTA*. In a placebo-controlled study in subjects with a history of, or an increased risk of, cardiovascular disease, there was no increase in the risk of, cardiovascular events, serious cardiovascular events, or adjudicated cardiovascular deaths in patients receiving Fluticasone furoate/Vilanterol compared with placebo (see *Adverse Reactions*). However, *RELVAR ELLIPTA* should be used with caution in patients with severe cardiovascular disease.

Patients with hepatic impairment
For patients with moderate to severe hepatic impairment, the 100/25 micrograms dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions (see *Pharmacokinetics*).

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, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

As with all medication containing corticosteroids, *RELVAR ELLIPTA* should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

Pneumonia
An increase in pneumonia has been observed in patients with COPD receiving *RELVAR ELLIPTA*. There was also an increased incidence of pneumonias resulting in hospitalisation. In some incidences these pneumonia events were fatal (see *Clinical studies and Adverse Reactions*). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD receiving *RELVAR ELLIPTA* include current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m^2 and patients with a (forced expiratory volume) FEV_1<50% predicted. These factors should be considered when Fluticasone furoate/Vilanterol is prescribed and treatment should be re-evaluated if pneumonia occurs.

The incidence of pneumonia in patients with asthma was common at the higher dose. Patients with asthma taking Fluticasone furoate/Vilanterol 200/25 micrograms may be at an increased risk of pneumonia compared with those receiving Fluticasone furoate/Vilanterol 100/25 or placebo. No risk factors were identified.

Immunosuppression
Persons 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 children or adults using corticosteroids. In such children or adults 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.

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

Hyperglycaemia
There have been reports of increases in blood glucose levels in diabetic patients and this should be considered when prescribing to patients with a history of diabetes mellitus.

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

Interaction with beta-blockers
Beta-adrenergic blockers may weaken or antagonise the effect of $beta_2$-adrenergic agonists. Concurrent use of both non-selective and selective beta-blockers should be avoided unless there are compelling reasons for their use.

Interaction with CYP3A4 inhibitors
Fluticasone furoate and Vilanterol are both 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 both Fluticasone furoate and Vilanterol, which could lead to an increase in the potential for adverse reactions and concomitant use should be avoided. 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 mg). 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 hours weighted mean serum cortisol. Co-administration increased mean Vilanterol $AUC_{(0-t)}$ and C_{max} 65% and 22%, respectively. The increase in Vilanterol exposure was not associated with an increase in $beta_2$-agonist related systemic effects on heart rate, blood potassium or QTcF interval.

Interaction with P-glycoprotein inhibitors
Fluticasone furoate and Vilanterol are both substrates of P-glycoprotein (P-gp). A clinical pharmacology study in healthy subjects with co-administered Vilanterol and the potent P-gp and moderate CYP3A4 inhibitor Verapamil did not show any significant effect on the pharmacokinetics of Vilanterol. Clinical pharmacology studies with a specific P-gp inhibitor and Fluticasone furoate have not been conducted.

Sympathomimetic medicinal products
Concomitant administration of other sympathomimetic medicinal products (alone or as part of combination therapy) may potentiate the adverse reactions of Fluticasone furoate/Vilanterol. *RELVAR ELLIPTA* should not be used in conjunction with other long-acting $beta_2$-adrenergic agonists or medicinal products containing long-acting $beta_2$-adrenergic agonists.

3.6 Pregnancy and Lactation Fertility

There are no fertility data in humans. Animal studies showed no effect of Vilanterol or Fluticasone furoate on fertility *(*see *Pre-clinical Safety Data section).*

Pregnancy
There has been limited pregnancy exposure in humans.

Animal studies have shown reproductive toxicity after administration of $beta_2$-agonists and corticosteroids (see *Pre-clinical Safety Data section*).

Administration of Fluticasone furoate/Vilanterol to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Lactation
There is limited information on the excretion of Fluticasone furoate or Vilanterol or their metabolites in human milk. However, other corticosteroids and $beta_2$-agonists are detected in human milk (see *Pre-clinical Safety Data section*). A risk to breastfed newborns/infants cannot be excluded.

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

3.7 Effects on Ability to Drive and Use Machines

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

3.8 Adverse Reactions Clinical trial data

Data from large asthma and COPD clinical trials were used to determine the frequency of adverse reactions associated with *RELVAR ELLIPTA*. In the asthma clinical development program a total of 7,034 patients were included in an integrated assessment of adverse reactions. In the COPD clinical development program a total of 6,237 subjects were included in an integrated assessment of adverse reactions.

With the exception of pneumonia and fractures, the safety profile was similar in patients with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently observed in patients with COPD.

These adverse reactions are listed by system organ class and frequency. The following convention has been

used for the classification of adverse reactions:

Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000

System organ class	Adverse reaction(s)	Frequency
Infections and infestations	Pneumonia*, Upper Respiratory Tract Infection, Bronchitis, Influenza, Candidiasis of mouth and throat	Common
Nervous system disorders	Headache	Very Common
Cardiac disorders	Extrasystoles**	Uncommon
Respiratory, thoracic & mediastinal disorders	Nasopharyngitis Oropharyngeal pain, Sinusitis, Pharyngitis, Rhinitis, Cough, Dysphonia	Very Common Common
Gastrointestinal disorders	Abdominal pain	Common
Musculoskeletal and connective tissue disorders	Arthralgia, Back pain Fractures***	Common
General disorders and administration site conditions	Pyrexia	Common

Description of selected adverse reactions

*Pneumonia (see *Warnings and Precautions*)

In two replicate 12 month studies in a total of 3,255 patients with COPD (mean post-bronchodilator screening FEV_1 45% of predicted, standard deviation (SD) 13%) who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia (6%-7%) reported in patients receiving the Fluticasone furoate (at strengths of 50, 100, and 200 micrograms)/Vilanterol 25 micrograms combination than in those receiving Vilanterol 25 micrograms alone (3%). Pneumonia which required hospitalisation occurred in 3% of patients receiving *RELVAR ELLIPTA* (all strengths) and in <1% of patients receiving Vilanterol. In these studies, nine fatal cases of pneumonia were reported. Of these, seven were reported during treatment with *RELVAR ELLIPTA* 200/25 micrograms, one during treatment with *RELVAR ELLIPTA* 100/25 micrograms and one post-treatment with Vilanterol monotherapy. The number of pneumonia events per 1,000 patient years was 97.9 with FF/VI 200/25, 85.7 in the FF/VI 100/25 and 42.3 in the VI 25 group. For severe pneumonia, the corresponding numbers of events per 1,000 patient years were 33.6, 35.5, and 7.6 respectively, while for serious pneumonia, the corresponding events per 1,000 patient years were 35.1 for FF/VI 200/25, 42.9 with FF/VI 100/25, 12.1 with VI 25. Finally, the exposure-adjusted cases of fatal pneumonia were 8.8 for FF/VI 200/25 versus 1.5 for FF/VI 100/25 and 0 for VI 25.

In SUMMIT, a multi-centre, randomised study (HZC113782), 16,568 subjects received Fluticasone furoate/Vilanterol 100/25 micrograms, Fluticasone furoate 100 micrograms, Vilanterol 25 micrograms, or placebo for a mean of 1.7 years. Subjects had moderate COPD (mean post- bronchodilator screening FEV1 60% of predicted, SD 6%) and a history of, or an increased risk of, cardiovascular disease. The adverse events of pneumonia are noted in the table below.

On-treatment Events	Number (%) of Subjects [Event Rate Per 1,000 Treatment Years]			
	FF/VI 100/25 N=4,140	FF 100 N=4,157	VI 25 N=4,140	Placebo N=4,131
Pneumonia	237 (6)	228 (5)	163 (4)	214 (5)
	[39.5]	[42.4]	[27.7]	[38.4]
Serious pneumonia	140 (3)	146 (4)	104 (3)	127 (3)
	[22.4]	[25.1]	[16.4]	[22.2]
Adjudicated pneumonia deaths	13 (<1)	10 (<1)	6 (<1)	9 (<1)
	[1.8]	[1.5]	[0.9]	[1.4]

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of pneumonia (adjusted for exposure, due to low numbers and limited number of patients on placebo) seen with *RELVAR ELLIPTA* 100/25 microgram strength (9.6/1,000 patient years) was similar to placebo (8.0/1,000 patient years). There was a higher incidence of pneumonia in the 200/25 microgram strength (18.4/1,000 patient years) compared to the 100/25 microgram strength. Few of the pneumonia events led to hospitalisation with either strength, and there were no observed differences in the incidence of serious events between the two treatment strengths.

**Cardiovascular events (see *Warnings and Precautions*)
For the SUMMIT study (see description above), the annualised event rate (per 1,000 treatment- years) of serious cardiovascular events was 64.5 for Fluticasone furoate/Vilanterol 100/25, 58.1 for Fluticasone furoate 100 micrograms, 59.2 for Vilanterol 25 micrograms, and 63.2 for placebo. The annualised event rate (per 1,000 treatment years) for adjudicated cardiovascular deaths was 11. 7 for Fluticasone furoate/Vilanterol 100/25, 11.6 for Fluticasone furoate 100 micrograms, 12.9 for Vilanterol 25 micrograms, and 13.0 for placebo.

***Fractures
In two replicate 12 month studies in a total of 3,255 patients with COPD the incidence of bone fractures overall was low in all treatment groups, with a higher incidence in all *RELVAR ELLIPTA* groups (2%) compared with the Vilanterol 25 micrograms group (<1%). Although there were more fractures in the *RELVAR ELLIPTA* groups compared with the Vilanterol 25 micrograms group, fractures typically associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of the *RELVAR ELLIPTA* and Vilanterol treatment arms.

For the SUMMIT study (see description above), fractures are noted in the table below

On-treatment Events	**Number (%) of Subjects [Event Rate Per 1,000 Treatment Years]**			
	FF/VI 100/25 N=4,140	**FF 100 N=4,157**	**VI 25 N=4,140**	**Placebo N=4,131**
All fractures	82 (2)	66 (2)	74 (2)	69 (2)
	[13.6]	[12.8]	[13.2]	[11.5]
Fractures commonly associated with ICS use	23 (<1)	24 (<1)	17 (<1)	13 (<1)
	[3.4]	[3.9]	[2.4]	[2.1]

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures was <1%, and usually associated with trauma.

Post-marketing data

System organ class	**Adverse reaction(s)**	**Frequency**
Immune system disorders	Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria.	Rare
Psychiatric disorders	Anxiety	Rare
Nervous system disorders	Tremor	Rare
Cardiac disorders	Palpitations, Tachycardia	Rare Rare
Musculoskeletal and connective tissue disorders	Muscle spasms	Common
Respiratory, thoracic and mediastinal disorders	Paradoxical bronchospasm	Rare

Adverse events should be reported to GSK Indonesia via website https://gsk.public.reportum.com and Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan.
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id

3.9 Overdose
Symptoms and signs
There are no data available from clinical trials on overdose with *RELVAR ELLIPTA*.

An overdose of *RELVAR ELLIPTA* may produce signs and symptoms due to the individual components' actions, including those seen with overdose of other beta$_2$-agonists and consistent with the known inhaled corticosteroid class effects (see *Warnings and Precautions*).

Treatment
There is no specific treatment for an overdose with *RELVAR ELLIPTA*. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Cardioselective beta-blockade should only be considered for profound Vilanterol overdose effects that are clinically concerning and unresponsive to supportive measures. Cardioselective beta-blocking drugs should be used with caution in patients with a history of bronchospasm.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamics Mechanism of action
Fluticasone furoate and Vilanterol represent two classes of medications (a synthetic corticosteroid and a selective, long-acting beta$_2$-receptor agonist).

Pharmacodynamic effects
Fluticasone furoate:
Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent anti inflammatory activity. The precise mechanism through which Fluticasone furoate affects asthma and COPD 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).

Vilanterol trifenatate:
Vilanterol trifenatate is a selective long-acting, beta$_2$-adrenergic agonist (LABA).

The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including Vilanterol trifenatate, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Molecular interactions occur between corticosteroids and LABAs, whereby steroids activate the beta$_2$-receptor gene, increasing receptor number sensitivity; and LABAs prime the glucocorticoid receptor for steroid-dependent activation and enhance cell nuclear translocation. These synergistic interactions are reflected in enhanced anti-inflammatory activity, which has been demonstrated *in vitro* and *in vivo* in a range of inflammatory cells relevant to the pathophysiology of both asthma and COPD. Airway biopsy studies have also shown the synergy between corticosteroids and LABAs to occur at clinical doses of the drugs in patients with COPD.

4.2 Pharmacokinetics Absorption
The absolute bioavailability for Fluticasone furoate and Vilanterol when administered by inhalation as *RELVAR ELLIPTA* was on average 15.2% and 27.3%, respectively. The oral bioavailability of both Fluticasone furoate and Vilanterol was low, on average 1.26% and <2%, respectively. Given this low oral bioavailability, systemic exposure for Fluticasone furoate and Vilanterol following inhaled administration is primarily due to absorption of the inhaled portion of the dose delivered to the lung.

Distribution
Following intravenous dosing, both Fluticasone furoate and Vilanterol are extensively distributed with average volumes of distribution at steady state of 661 L and 165 L, respectively.

Both Fluticasone furoate and Vilanterol have a low association with red blood cells. In vitro plasma protein binding in human plasma of Fluticasone furoate and Vilanterol was high, on average >99.6% and 93.9%, respectively. There was no decrease in the extent of in vitro plasma protein binding in subjects with

renal or hepatic impairment.

Fluticasone furoate and Vilanterol are substrates for P-gp, however, concomitant administration of Fluticasone furoate/Vilanterol with P-gp inhibitors is considered unlikely to alter Fluticasone furoate or Vilanterol systemic exposure since they are both well absorbed molecules.

Metabolism
Based on *in vitro* data, the major routes of metabolism of both Fluticasone furoate and Vilanterol in human 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.

Vilanterol is primarily metabolised by O-dealkylation to a range of metabolites with significantly reduced β_1- and β_2-agonist activity.

A repeat dose CYP3A4 drug interaction study was performed in healthy subjects with the Fluticasone furoate/Vilanterol combination (200/25) and the strong CYP3A4 inhibitor Ketoconazole (400 mg). 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.

Co-administration increased mean Vilanterol $AUC_{(0-t)}$ and C_{max} 65% and 22%, respectively. The increase in Vilanterol exposure was not associated with an increase in beta-agonist related systemic effects on heart rate, blood potassium or QTcF interval.

Elimination
Following oral administration, Fluticasone furoate was eliminated in humans mainly by metabolism with metabolites being excreted almost exclusively in faeces, with <1% of the recovered radioactive dose eliminated in the urine. The apparent plasma elimination half-life of Fluticasone furoate following inhaled administration of Fluticasone furoate/Vilanterol was, on average, 24 hours.

Following oral administration, Vilanterol was eliminated in humans mainly by metabolism followed by excretion of metabolites in urine and faeces approximately 70% and 30% of the radioactive dose respectively. The apparent plasma elimination half-life of Vilanterol following inhaled administration of Fluticasone furoate/Vilanterol was, on average, 2.5 hours. The effective half-life for accumulation of Vilanterol, as determined from inhalation administration of repeat doses of Vilanterol 25 micrograms, is 16.0 hours in subjects with asthma and 21.3 hours in subjects with COPD.

Special Patient Populations
Population PK meta-analyses for Fluticasone furoate and Vilanterol were conducted in phase III studies in subjects with asthma or COPD. The impact of demographic covariates (age, gender, weight, BMI, racial group, ethnicity) on the pharmacokinetics of Fluticasone furoate and Vilanterol were evaluated as part of the population pharmacokinetic analysis.

Race
In subjects with asthma or COPD estimates of Fluticasone furoate $AUC_{(0-24)}$ for East Asian, Japanese and South East Asian subjects (12-14% subjects) were up to 53% higher on average compared with Caucasian subjects. However, there was no evidence for the higher systemic exposure in these populations to be associated with greater effect on 24 hour urinary cortisol excretion. There was no effect of race on pharmacokinetic parameter estimates of Vilanterol in subjects with COPD.

On average, Vilanterol Cmax is estimated to be 220 to 287% higher and $AUC_{(0-24)}$ comparable for those subjects from an Asian heritage compared with subjects from other racial groups. However, there was no evidence that this higher Vilanterol C_{max} resulted in clinically significant effects on heart rate.

Children
In adolescents (12 years or older), there are no recommended dose modifications.

The pharmacokinetics of Fluticasone furoate/Vilanterol in patients less than 12 years of age has not been studied. The safety and efficacy of Fluticasone furoate/Vilanterol in children under the age of 12 years has not yet been established.

Elderly
The effects of age on the pharmacokinetics of Fluticasone furoate and Vilanterol were determined in phase III studies in COPD and asthma.

There was no evidence for age (12-84) to affect the PK of Fluticasone furoate and Vilanterol in subjects with asthma.

There was no evidence for age to affect the PK of Fluticasone furoate in subjects with COPD while there was an increase (37%) in $AUC_{(0-24)}$ of Vilanterol over the observed age range of 41 to 84 years. For an elderly subject (aged 84 years) with low bodyweight (35 kg) Vilanterol $AUC_{(0-24)}$ is predicted to be 35% higher than the population estimate (subject with COPD aged 60 years and bodyweight of 70 kg), whilst C_{max} was unchanged. These differences are unlikely to be of clinical relevance.

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 Vilanterol or more marked corticosteroid or $beta_2$-agonist 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. The increase in Fluticasone furoate systemic exposure (Fluticasone furoate/Vilanterol 200/25 micrograms) in subjects with moderate hepatic impairment (Child-Pugh B) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. In subjects with severe hepatic impairment (Child-Pugh C) that received a lower dose of 100/12.5 micrograms there was no reduction in serum cortisol. For patients with moderate or severe hepatic impairment the maximum dose is 100/25 micrograms (see *Dosage and Administration*).

Following repeat dosing of Fluticasone furoate/Vilanterol for 7 days, there was no significant increase in systemic exposure to Vilanterol (C_{max} and AUC) in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh A, B or C).

There were no clinically relevant effects of the Fluticasone furoate/Vilanterol combination on beta-adrenergic systemic effects (heart rate or serum potassium) in subjects with mild or moderate hepatic impairment (Vilanterol, 25 micrograms) or with severe hepatic impairment (Vilanterol, 12.5 micrograms) compared with healthy subjects.

Gender, Weight and BMI
There was no evidence for gender, weight or BMI to influence the pharmacokinetics of Fluticasone furoate based on a population pharmacokinetic analysis of phase III data in 1,213 subjects with asthma (712 females) and 1,225 subjects with COPD (392 females).

There was no evidence for gender, weight or BMI to influence the pharmacokinetics of Vilanterol based on a population pharmacokinetic analysis in 856 subjects with asthma (500 females) and 1,091 subjects with COPD (340 females).

No dosage adjustment is necessary based on gender, weight or body mass index (BMI).

4.3 Clinical Studies
RELVAR ELLIPTA clinical studies Asthma
The safety and efficacy of Fluticasone furoate (FF) and Vilanterol (VI) in the treatment of asthma has been evaluated in 3 randomised, double-blind clinical trials of between 12 to 76 weeks in duration (HZA106827, HZA106829 and HZA106837) involving 3,210 patients 12 years of age and older with persistent asthma.

All subjects were using an ICS (Inhaled Corticosteroid) with or without LABA for at least 12 weeks prior to Visit 1. In HZA106837 all patients had at least one exacerbation that required treatment with oral corticosteroids in the year prior to Visit 1. Results for HZA106827 and HZA106829 are shown in the table below:

Summary of Data from Studies HZA106829 and HZA106827

Study No.	HZA106829	HZA106827		
	RELVAR ELLIPTA 200/25OD* vs FF 200 OD	*RELVAR ELLIPTA* 100/25 OD vs FF 100 OD	*RELVAR ELLIPTA* 100/25 OD vs placebo OD	FF 100 OD vs placebo OD
Change from Baseline in Trough FEV1 (mL)				
Treatment difference (95% CI) p-value	193 (108, 277) p<0.001	36 (-48, 120) p=0.405	172 (87, 258) p<0.001	136 mL (51, 222) p=0.002
Weighted Mean Serial FEV_1 over 0-24 hours post-dose (mL)				
Treatment difference (95% CI) p-value	136 (1, 270) p=0.048	116 (-5, 236) p=0.06	302 (178, 426) p<0.001	186 mL (62, 310) p=0.003
Change from Baseline in Rescue–free 24 hour periods				
Treatment difference (95% CI) p-value	11.7% (4.9, 18.4) p<0.001	10.6% (4.3, 16.8) p<0.001	19.3% (13.0, 25.6) p<0.001	8.7% (2.4, 15.0) p=0.007

*OD = Once Daily

HZA106837 was of variable treatment duration (from a minimum of 24 weeks to a maximum of 76 weeks with the majority of patients treated for at least 52 weeks) and compared *RELVAR ELLIPTA* 100/25 micrograms [N=1009] and FF 100 micrograms [N=1010]. The primary endpoint was the time to first severe asthma exacerbation (a severe asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroids or an inpatient hospitalisation or emergency department visit.

The risk of experiencing a severe asthma exacerbation in patients receiving *RELVAR ELLIPTA* 100/25 was reduced by 20% compared with FF 100 alone (hazard ratio 0.795, p=0.036 95% CI (0.642, 0.985)). The rate of severe asthma exacerbations per patient per year was 0.19 in the FF 100 group and 0.14 in the *RELVAR ELLIPTA* 100/25 group. The ratio of the exacerbation rate for *RELVAR ELLIPTA* 100/25 versus FF 100 was 0.755 (95% CI 0.603, 0.945). This represents a 25% reduction in the rate of severe asthma exacerbations for subjects treated with *RELVAR ELLIPTA* 100/25 compared with FF 100 (p=0.014). The 24-hour bronchodilator effect of *RELVAR ELLIPTA* was maintained throughout a one-year treatment period with no evidence of loss in efficacy (no tachyphylaxis). *RELVAR ELLIPTA* 100/25 micrograms consistently demonstrated 83 mL to 95 mL improvements in trough FEV_1 at Weeks 12, 36 and 52 and Endpoint compared with FF 100 (p<0.001 95% CI 52, 126 mL at Endpoint). Forty four percent of patients in the *RELVAR ELLIPTA* 100/25 group were well controlled (ACQ7 ≤0.75) at end of treatment compared to 36% of subjects in the FF 100 group (p<0.001 95% CI 1.23, 1.82).

Chronic Obstructive Pulmonary Disease

The efficacy of Fluticasone furoate and Vilanterol in the treatment of patients with COPD has been evaluated in two 6-month (HZC112206, HZC112207) and two one-year randomised controlled studies (HZC102970, HZC102871), and one long-term study (SUMMIT) in patients with a clinical diagnosis of COPD.

Six month studies

HZC112206 and HZC112207 were 24 week randomised, double-blind, placebo controlled, parallel group studies comparing the effect of the combination to Vilanterol and FF alone and placebo. HZC112206 evaluated the efficacy of *RELVAR ELLIPTA* 50/25 micrograms [n=206] and *RELVAR ELLIPTA* 100/25 micrograms [n=206]) compared with FF (100 micrograms [n=206]) and Vilanterol (25 micrograms [n=205]) and placebo (n=207), all administered once daily.

HZC112207 evaluated the efficacy of *RELVAR ELLIPTA* 100/25 micrograms [n=204] and *RELVAR ELLIPTA* 200/25 [n=205]) compared with FF (100 micrograms [n=204] and 200 micrograms [n=203]) and Vilanterol (25 micrograms [n=203]) and placebo (n=205), all administered once daily.

The co-primary endpoints in both studies were the weighted mean FEV_1 from zero to 4 hours post- dose and change from baseline in pre-dose trough FEV1 at the end of the study.

In an integrated analysis of both studies, *RELVAR ELLIPTA* 100/25 micrograms showed clinically meaningful improvements in lung function. At the 24-week time point *RELVAR ELLIPTA* 100/25 micrograms and Vilanterol increased trough FEV_1 by 129 mL (95% CI 91, 167 mL, p<0.001) and 83 mL (95% CI 46, 121 mL, p<0.001) respectively compared with placebo. *RELVAR ELLIPTA* 100/25 micrograms increased trough FEV_1 by 46 mL compared with Vilanterol (95% CI 8, 83 mL, p= 0.017).

At the 24-week time point *RELVAR ELLIPTA* 100/25 micrograms and Vilanterol had a higher weighted mean FEV_1 over 0-4 hours of 193 mL (95% CI 156, 230 mL, p<0.001) and 145 mL (95% CI 108, 181 mL,

p<0.001) respectively compared with placebo. The difference in weighted mean FEV_1 over 0-4 hours between the Fluticasone furoate/Vilanterol 100/25 and Vilanterol groups was 48 mL (95% CI 12, 84 mL, p= 0.009).

12 months studies

Studies HZC102970 and HZC102871 were 52 week randomised, double-blind, parallel-group, studies comparing the efficacy and safety of *RELVAR ELLIPTA* 200/25 micrograms, *RELVAR ELLIPTA* 100/25 micrograms, Fluticasone furoate/Vilanterol 50/25 micrograms and Vilanterol 25 micrograms, all administered once daily. The primary endpoint was the reduction in the annual rate of moderate and severe exacerbations in subjects with COPD.

The results of both studies showed that treatment with *RELVAR ELLIPTA* 100/25 micrograms once daily resulted in a 27% reduction in the annual rate of moderate or severe COPD exacerbations compared with Vilanterol (95% CI:16, 37% (p≤0.001). Similar reductions in the time to first exacerbation and exacerbations requiring systemic corticosteroid use were observed with Fluticasone furoate/Vilanterol 100/25 micrograms once daily.

In a pooled analysis of HZC102970 and HZC102871, at Week 52, the *RELVAR ELLIPTA* 100/25 microgram group demonstrated greater improvement in trough FEV1 compared with the Vilanterol 25 microgram group (a difference of 42 mL in adjusted mean change from baseline; 95% CI: 19, 64 mL, p<0.001).

Long-term study

SUMMIT was a multi-centre, randomised, double-blind study evaluating the effect on survival of Fluticasone furoate/Vilanterol 100/25 micrograms compared with placebo. 16,590 patients were randomised and of these, 16,485 subjects were included in the intent-to-treat efficacy population. Subjects were treated for up to 4 years (mean 1.7 years) with either Fluticasone furoate/Vilanterol 100/25 micrograms, Fluticasone furoate 100 micrograms, Vilanterol 25 micrograms, or placebo. All subjects had COPD with moderate airflow limitation (≥50% and ≤70% predicted FEV1) and a history of, or an increased risk of, cardiovascular (CV) disease. The primary endpoint was all-cause mortality, while secondary endpoints were a composite of cardiovascular events (on treatment cardiovascular death, myocardial infarction, stroke, unstable angina, or transient ischemic attack) and the rate of decline in post-bronchodilator FEV_1. In the year prior to study start, 39% of subjects experienced at least one COPD exacerbation and 15% experienced 2 or more COPD exacerbations. Prior to the start of the study, 35% of subjects were taking long-acting $beta_2$-agonists and 15% were taking long-acting anticholinergic medications - these medications were stopped prior to study entry per protocol. The patient baseline characteristics described above are provided in the table below per treatment arm:

Summary of Baseline Characteristics from Study HZC113782 (SUMMIT)

Baseline characteristic	**FF/VI 100/25**	**FF 100**	**VI 25**	**Placebo**
	N=4,121	**N=4,135**	**N=4,118**	**N=4,111**
COPD exacerbation history, n (%)				
0	2,528 (61)	2,546 (62)	2,500 (61)	2,447 (60)
1	998 (24)	990 (24)	988 (24)	1,044 (25)
≥2	595 (14)	599 (14)	630 (15)	620 (15)
Baseline medications, n (%)				
Long-acting $beta_2$-agonist	1,456 (35)	1,432 (35)	1,464 (36)	1,417 (34)
Long-acting anticholinergic	638 (15)	619 (15)	634 (15)	659 (16)
Inhaled corticosteroids	1,394 (34)	1,369 (33)	1,374 (33)	1,349 (33)

All-cause mortality was not statistically significantly different between placebo and Fluticasone furoate/Vilanterol (HR 0.878; 95% CI: 0.739, 1.042). All-cause mortality (per 100 patient-years) was 3.1 for Fluticasone furoate/Vilanterol, 3.5 for placebo, 3.2 for Fluticasone furoate, and 3.4 for Vilanterol.

The mean rate of decline in FEV_1 was Fluticasone furoate/Vilanterol, 38 mL/year; placebo, 46 mL/year; Fluticasone furoate, 38 mL/year; and Vilanterol, 47 mL/year.

The incidence of cardiovascular composite events (per 100 patient-years of treatment exposure) was 2.5 for Fluticasone furoate/Vilanterol, 2.7 for placebo, 2.4 for Fluticasone furoate, and 2.6 for Vilanterol.

The annual rate of severe exacerbations per patient per year (requiring hospitalisation) was 0.05 for Fluticasone furoate/Vilanterol, 0.07 for placebo, 0.06 for Fluticasone furoate, and 0.06 for Vilanterol.

Summary of Efficacy Data from Study HZC113782 (SUMMIT)

Efficacy endpoint	FF/VI 100/25	FF 100	VI 25	Placebo
	N=4,121	N=4,135	N=4,118	N=4,111
All-cause mortality (per 100 patient-years)	3.1	3.2	3.4	3.5
FEV1 decline (mL/year)	38	38	47	46
Cardiovascular composite endpoint (per 100 patient-years of treatment exposure)	2.5	2.4	2.6	2.7
Annual rate of severe exacerbations per patient per year (requiring hospitalisation)	0.05	0.06	0.06	0.07

4.4 Pre-clinical Safety Data

Pharmacological and toxicological effects seen with Fluticasone furoate or Vilanterol in non-clinical studies were those typically associated with either glucocorticoids or beta$_2$-agonists. Administration of Fluticasone furoate combined with Vilanterol did not result in any significant new toxicity.

Carcinogenesis/mutagenesis

Fluticasone furoate was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in rats or mice at exposures similar to those at the maximum recommended human dose, based on AUC.

Genetic toxicity studies indicate Vilanterol does not represent a genotoxic hazard to humans. Consistent with findings for other beta$_2$-agonists, in lifetime inhalation studies Vilanterol caused proliferative effects in the female rat and mouse reproductive tract and rat pituitary gland. There was no increase in tumour incidence in rats or mice at exposures 2- or 30-fold, respectively, those at the maximum recommended human dose, based on AUC.

Reproductive Toxicology

Effects seen following inhalation administration of Fluticasone furoate in combination with Vilanterol in rats were similar to those seen with Fluticasone furoate alone.

Fluticasone furoate was not teratogenic in rats or rabbits, but delayed development in rats and caused abortion in rabbits at maternally toxic doses. There were no effects on development in rats at exposures approximately 3-times greater than those at the maximum recommended human dose, based on AUC.

Vilanterol was not teratogenic in rats. In inhalation studies in rabbits, Vilanterol caused effects similar to those seen with other beta$_2$-agonists (cleft palate, open eyelids, sternebral fusion and limb flexure/malrotation). When given subcutaneously there were no effects at exposures 84-times greater than those at the maximum recommended human dose, based on AUC.

Neither Fluticasone furoate nor Vilanterol had any adverse effects on fertility or pre- and post-natal development in rats.

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Lactose monohydrate (which contains milk protein)
(12.5 milligram Lactose monohydrate per blister)

Magnesium stearate

5.2 Incompatibilities

None.

5.3 Shelf Life

The expiry date is indicated on the packaging.

In-use shelf-life
The In-use shelf-life depends on the locally registered storage conditions (refer to the pack for information).

Following removal from the tray, the product may be stored for a maximum period of: 1 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.

5.4 Special Precautions for Storage
Storage condition depends on local registration requirements.

Store below 30°C.

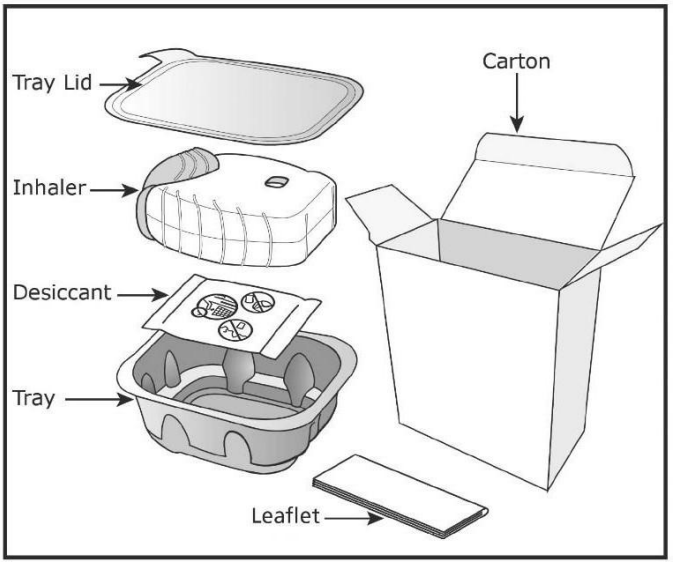
If stored in the refrigerator, allow the inhaler to return to room temperature for at least an hour before use.

5.5 Nature and Contents of Container
The plastic Ellipta inhaler consists of a light grey body, a pale blue 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.

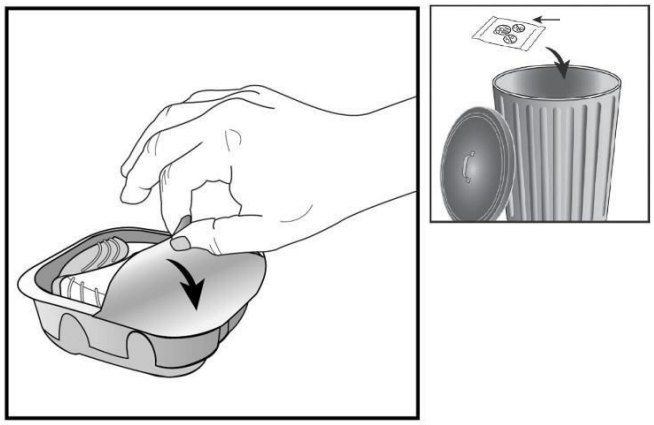
The inhaler contains two strips of 30 regularly distributed blisters, each containing a white powder.

5.6 Instructions for Use/Handling
When you first use the Ellipta inhaler you do not need to check that it is working properly. It is ready for use straightaway, 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 sachet away — **don't** open, eat, or inhale it.



When you take the inhaler out of its box, 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.

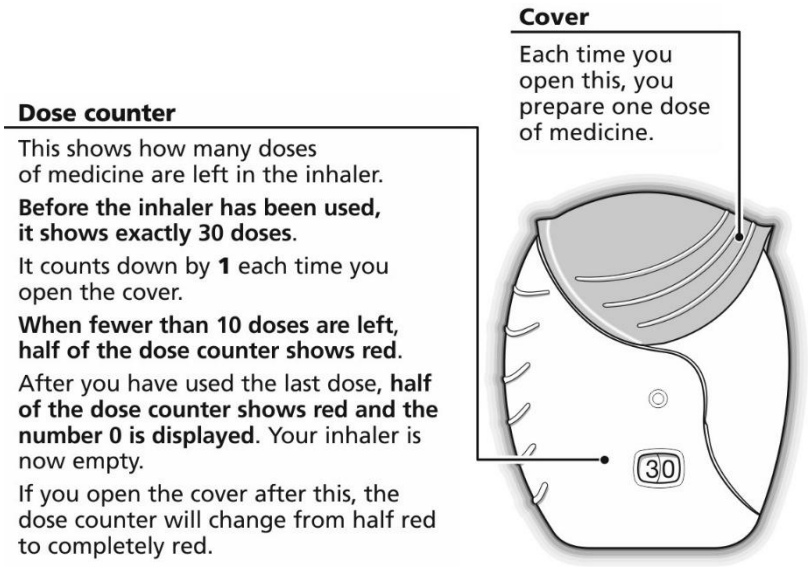
For market with registered storage condition of 30°C, the "Discard by" date is 1 month from the date you first open the tray. **After this date, the inhaler should no longer be used**.

a) 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.

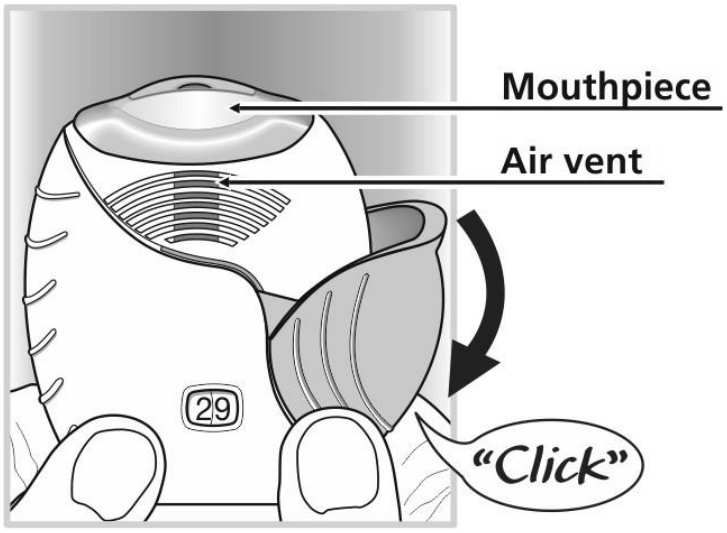


b) Prepare a dose

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.

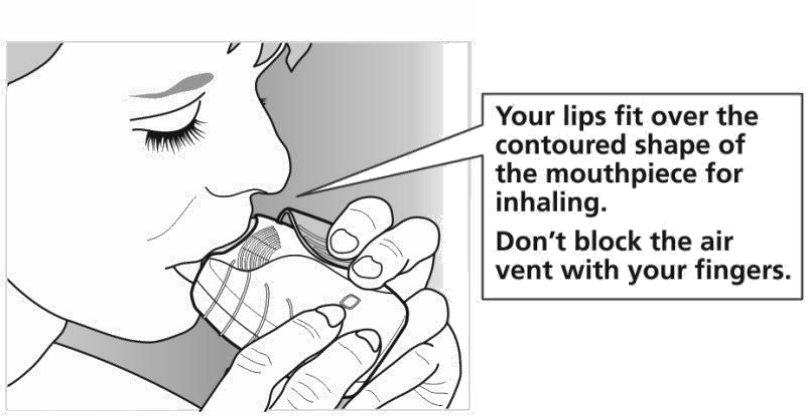
- **If the dose counter does not count down as you hear the "click", the inhaler will not deliver medicine. Take it back to your pharmacist for advice.**

- **Do not shake the inhaler at any time.**

c) 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).**

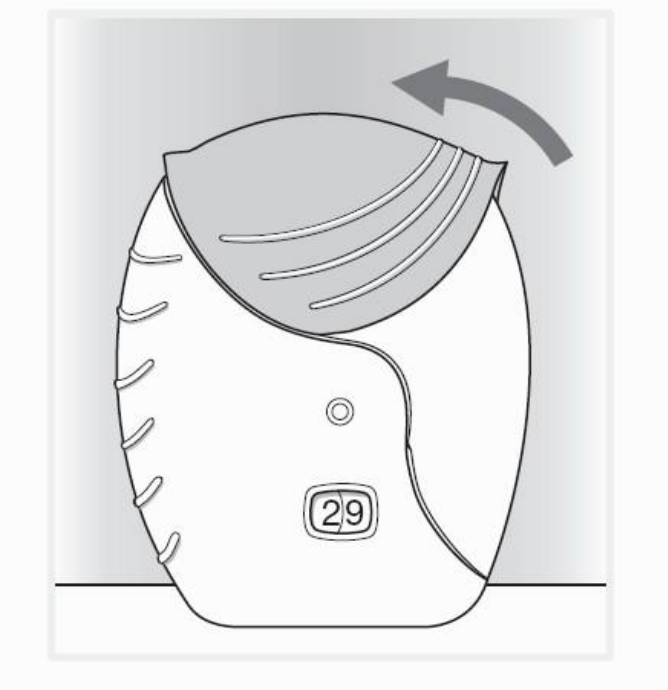
- **Remove the inhaler from your mouth.**

- **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.

d) 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 after you have used the inhaler.**

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

HARUS DENGAN RESEP DOKTER

RELVAR ELLIPTA 100/25, Box, 1 Ellipta inhaler @ 30 doses Reg. No. DKI1875705067A1
RELVAR ELLIPTA 200/25, Box, 1 Ellipta inhaler @ 30 doses Reg. No. DKI1875705067B1

Manufactured by
Glaxo Operations UK Ltd Trading as Glaxo Wellcome Operations
Ware, United Kingdom

Imported by
PT Glaxo Wellcome Indonesia Jakarta, Indonesia

INNOVIVA

Version number : 01
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Date of local revision : 19 Dec 2025