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STRIVERDI® RESPIMAT®
Olodaterol

COMPOSITION

The STRIVERDI• RESPIMAT• is a soft mist inhaler delivering olodaterol inhalation solution.

The delivered dose is 2.5 microgram olodaterol per puff (2 puffs comprise one medicinal dose) and is equivalent to 2.7 microgram olodaterol hydrochloride.
(INN = olodaterol)

The delivered dose is the dose which is available for the patient after passing the mouthpiece.

Excipients**
Benzalkonium chloride, disodium edetate, water, purified, citric acid (anhydrous)

INDICATIONS

STRIVERDI• RESPIMAT• is indicated as long-term once daily maintenance bronchodilator treatment to improve lung function in patients with COPD.

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 5 microgram olodaterol given as two puffs from the RESPIMAT once-daily at the same time of the day. Do not use STRIVERDI• RESPIMAT• more than two inhalations every 24 hours *(see Instructions for use)*.

SPECIAL POPULATIONS

Elderly
Elderly patients can use STRIVERDI• RESPIMAT• at the recommended dose.

Paediatric population
COPD does not normally occur in children. The safety and effectiveness of STRIVERDI• RESPIMAT• in the pediatric population have not been established.

Patients with hepatic insufficiency
Patients with mild and morderate hepatic impairment can use STRIVERDI• RESPIMAT• at the recommended dose.

There are no data available for use of STRIVERDI• RESPIMAT• in patients with servere hepatic impairment.

Patients with renal insufficiency
Renally impaired patients can use STRIVERDI• RESPIMAT• at the recommended dose.

Instructions for use

STRIVERDI RESPIMAT is intended for oral inhalation only. The STRIVERDI RESPIMAT cartridge is only intended for use with the STRIVERDI RESPIMAT inhaler.

To ensure proper administration of STRIVERDI RESPIMAT, the patient should be shown how to use the STRIVERDI RESPIMAT inhaler by a physician or other health professional.

Introduction

STRIVERDI® RESPIMAT® (olodaterol). Read these Instructions for Use before you start using STRIVERDI® RESPIMAT® re-usable.

You will need to use this inhaler only ONCE A DAY. Each time you use it take TWO PUFFS.

- If not been used for more than 7 days release one puff towards the ground.
- If not been used for more than 21 days repeat steps 4 to 6 until a cloud is visible. Then repeat steps 4 to 6 three more times.

How to care for your STRIVERDI® RESPIMAT® re-usable

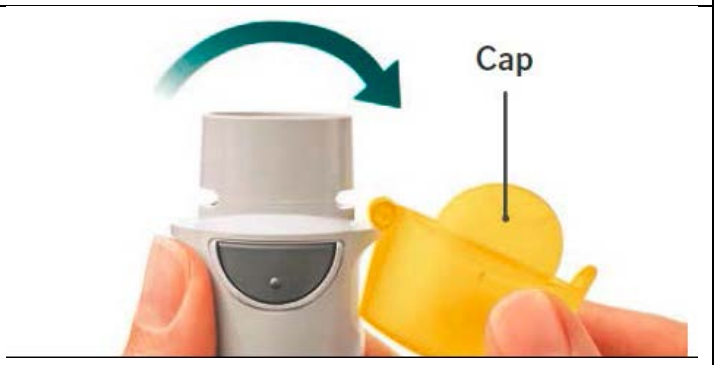
Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week. Any minor discoloration in the mouthpiece does not affect your STRIVERDI® RESPIMAT® re-usable inhaler performance. If necessary, wipe the outside of your STRIVERDI RESPIMAT re-usable inhaler with a damp cloth.

When to replace the inhaler

When you have used an inhaler with 6 cartridges, get a new STRIVERDI RESPIMAT re-usable pack containing an inhaler.

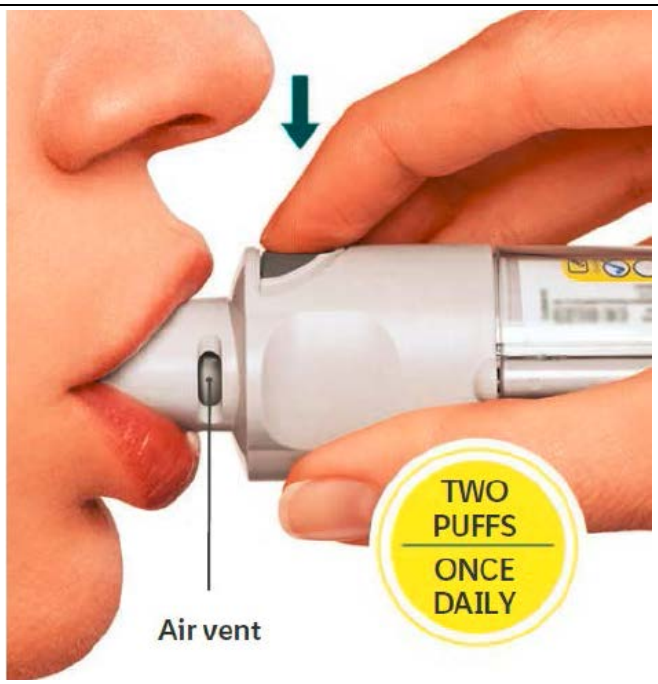
Prepare for first use

1. <u>Remove clear base</u> • Keep the cap closed. • Press the safety catch while firmly pulling off the clear base with your other hand.	
2. <u>Insert cartridge</u> • Insert the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it snaps into place.	
3. <u>Track cartridge and put clear base back</u> • Mark the check-box on inhaler's label to track the number of cartridges. • Put the clear base back into place until it clicks.	 

4. <u>Turn</u> • Keep the cap closed. • Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).	
5. Open • Open the cap until it snaps fully open.	
6. Press • Point the inhaler toward the ground • Press the dose-release button. • Close the cap. • Repeat steps 4-6 until a cloud is visible. • **After a cloud is visible**, repeat steps 4-6 three more times. Your inhaler is now ready to use and will deliver 60 puffs (30 doses).	

Daily use

TURN • Keep the cap closed. • **<u>TURN</u>** the clear base in the direction of the arrows on the label until it clicks (half a turn).	

OPEN • <u>OPEN</u> the cap until it snaps fully open.	
PRESS • Breathe out slowly and fully. • Close your lips around the mouthpiece without covering the air vents. Point your inhaler to the back of your throat. • While taking a slow, deep breath through your mouth, <u>PRESS</u> the dose-release button and continue to breathe in slowly for as long as comfortable. • Repeat Turn, Open, Press for a total of 2 puffs. • Close the cap until you use your inhaler again.	

When to replace the STRIVERDI RESPIMAT cartridge
The dose indicator shows how many puffs remain in the cartridge.

	60 puffs remaining
	Less than 10 puffs remaining. Obtain a new cartridge.
	Your cartridge is used up. Turn the clear base to loosen it. Your inhaler is now in a locked position. Pull off the cartridge from the inhaler. Insert a new cartridge until it clicks (refer to step 2). The new cartridge will stick out more than the very first cartridge (continue with step 3). Remember to put the clear base back to unlock the inhaler.

Answers to Common Questions

It is difficult to insert the cartridge deep enough.

Did you accidentally turn the clear base before inserting the cartridge? Open the cap, press the dose-release button, then insert the cartridge.
Are you replacing the cartridge? The new cartridge will stick out more than the very first cartridge. Insert it until it clicks, then replace the clear base.

I cannot press the dose-release button.
Did you put the clear base back? If not, put the clear base back to unlock the inhaler. The Respimat re-usable only functions with the clear base in place.

Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn).

Does the dose indicator on your cartridge display a white arrow on a red background? Your cartridge is used up. Insert a new cartridge.

It is difficult to remove the cartridge after it is used up.

Pull and turn the cartridge at the same time.

I cannot turn or put the clear base back.

Is the clear base loose and does the dose indicator on your cartridge display a white arrow on a red background? Your cartridge is used up. Insert a new cartridge.

Did you turn the clear base already?
If the clear base has already been turned, follow steps “OPEN” and “PRESS” under “Daily Use” to get your medicine.

My RESPIMAT re-usable has been used up too early

Did you use Respimat re-usable as indicated (two puffs/once daily)? Respimat will last 30 days if used at two puffs once daily.

Did you spray in the air often to check whether the Respimat re-usable is working? Once you have prepared Respimat re-usable, no test-spraying is required if used daily.

Did you take off and put the clear base multiple times back? Do not remove the clear base before the cartridge is used up. Each time you take off the clear base without cartridge exchange, the dose counter records one puff and the remaining doses are reduced.

My Respimat re-usable doesn’t spray.

Did you insert a cartridge? If not, insert a cartridge. If not, insert a cartridge. Once your RESPIMAT re-usable is assembled, do not remove the clear base or the cartridge until the cartridge is used up.
Did you repeat TURN, OPEN, PRESS less than three times after inserting the cartridge? Repeat TURN, OPEN, PRESS three times after inserting the cartridge as shown in the steps 4 to 6 under “Prepare for use”.

Does the dose indicator on your cartridge display a white arrow on a red background? Your cartridge is used up. Insert a new cartridge.

My RESPIMAT re-usable sprays automatically.

Was the cap open when you turned the clear base? Close the cap, then turn the clear base.
Did you press the dose-release button when turning the clear base? Close the cap, so the dose-release button is covered, then turn the clear base.

Did you stop when turning the clear base before it clicked? Turn the clear base in a continuous movement until it clicks (half a turn). The dose counter will count each incomplete turn and the number of remaining doses is reduced.

Was the cap open when you replaced the cartridge? Close the cap, then replace the cartridge.

CONTRAINDICATIONS

STRIVERDI® RESPIMAT® is contraindicated in patients with hypersensitivity to olodaterol or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS

Asthma

STRIVERDI® RESPIMAT® should not be used in asthma. The long-term effectiveness and safety of olodaterol in asthma have not been studied. Long-acting beta$_2$-adrenergic agonists (LABA) may increase the risk of asthma-related hospitalisations and death. Data from a large placebo-controlled study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including olodaterol, the active ingredient in STRIVERDI RESPIMAT.

Acute bronchospasm

STRIVERDI® RESPIMAT® is not indicated for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy.

Hypersensitivity

As with all medications, immediate hypersensitivity reactions may occur after administration of STRIVERDI® RESPIMAT®.

Deterioration of disease and acute episodes

STRIVERDI RESPIMAT should not be initiated in patients with acutely deteriorating COPD. In this case, the patient's COPD management plan should direct the patient to seek medical advice immediately, and a re-evaluation of the patient and the COPD treatment regimen should be undertaken. Increasing the daily dosage of STRIVERDI RESPIMAT beyond the recommended dose is not appropriate.

Paradoxical bronchospasm

As with other Inhaled medicines STRIVERDI® RESPIMAT® may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs STRIVERDI® RESPIMAT® should be discontinued immediately and alternative therapy substituted.

Systemic effects
Long acting beta$_2$-adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy and hypertension; in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval; and in patients who are unusually responsive to sympathomimetic amines.

Patients with a history of myocardial infarction during the previous year, unstable or life-threatening cardiac arrhythmia, hospitalized for heart failure during the previous year or with a diagnosis of paroxysmal tachycardia (>100 beats per minute) were excluded from the clinical trials. Therefore the experience in these patient groups is limited. STRIVERDI® RESPIMAT® should be used with caution in these patient groups.

Cardiovascular effects
Like other beta$_2$-adrenergic agonists, olodaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur, treatment may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave and ST segment depression, although the clinical significance of these observations is unknown.

Hypokalaemia
Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see section Interactions), which may increase the susceptibility to cardiac arrhythmias.

Hyperglycaemia
Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose.

STRIVERDI® RESPIMAT® should not be used in conjunction with any other medication containing long-acting beta$_2$-adrenergic agonists.
Patients who have been taking inhaled, short acting beta$_2$-adrenergic agonists on a regular basis (e.g. four times a day) should be instructed to use them only for symptomatic relief of acute respiratory symptoms.

Excipients
This medicine contains 0.0011 mg benzalkonium chloride in each actuation.
Benzalkonium chloride may cause wheezing and breathing difficulties. Patients with asthma are at an increased risk for these adverse events.

INTERACTIONS

Concomitant administration of other adrenergic agents may potentiate the undesirable effects of STRIVERDI® RESPIMAT®.

Xanthine Derivatives, Steroids or Diuretics
Concomitant treatment with xanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate any hypokalaemic effect of adrenergic agonists (see Special warnings and precautions).

Beta-blockers
Beta –adrenergic blockers may weaken or antagonise the effect of STRIVERDI® RESPIMAT®. Therefore STRIVERDI® RESPIMAT® should only be given together with beta-adrenergic blockers (including eye-drops) if there are compelling reasons for their use. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

MAO Inhibitors, Tricyclic Antidepressants, QTc prolonging drugs
Monamine oxidase inhibitors, or tricyclic antidepressants or other drugs known to prolong the QTc interval may potentiate the action of STRIVERDI® RESPIMAT® on the cardiovascular system.

Pharmacokinetic Drug Drug interactions
In a drug interaction study using the strong dual CYP and P-gp inhibitor ketoconazole a 1.7-fold increase of systemic exposure was observed (see section Pharmacokinetics). No safety concerns were identified in clinical studies of up to one year with STRIVERDI® RESPIMAT® at doses up to twice the recommended therapeutic dose. No dose adjustment is necessary.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy
For STRIVERDI® RESPIMAT® no clinical data on exposed pregnancies are available.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposures.

As with any medicine, use during pregnancy should only be considered if the expected benefit to the mother is greater than any risk to the foetus.
The inhibitory effect of beta-adrenergic agonists on uterine contraction should be taken into account.

Lactation
Clinical data from nursing women exposed to olodaterol are not available.

The substance and/or its metabolites have been detected in the milk of lactating rats, but no adverse effects on development or reproductive performance were seen in breast-fed pups at maternal inhalational doses up to 3,665 microgram/kg/day (plasma AUC approximately 3,000 times the anticipated AUC in adults). It is not known whether olodaterol passes into human breast milk.
Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with STRIVERDI® RESPIMAT® should be made taking into

account the benefit of breast-feeding to the child and the benefit of STRIVERDI® RESPIMAT® therapy to the woman.

Fertility
Clinical data on fertility are not available for STRIVERDI® RESPIMAT®. Preclinical studies performed with olodaterol showed no adverse effect on fertility (see section Toxicology).

No impairment of male or female fertility or early embryonic development was seen in the rat at inhalational doses up to approximately 3,000 microgram/kg/day (plasma AUC more than approximately 2,000 times the anticipated AUC in adults from a 5 microgram dose basis).

Driving and Using Machines

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that dizziness has been reported in clinical trials.Therefore, caution should be recommended when driving a car or operating machinery. If patients experience dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.

SIDE EFFECTS

The safety of STRIVERDI® RESPIMAT® has been evaluated in placebo- and active-controlled, parallel-group and cross-over clinical trials in overall 4,167 patients with COPD. A total of 1,927 patients with COPD received the target dose of 5 microgram olodaterol.

Side effects of STRIVERDI® RESPIMAT® were primarily identified from data obtained in 4 placebo-controlled, parallel-group, long-term treatment (48 weeks) clinical trials in COPD patients. Two of these trials were also active-comparator controlled.

Infections and infestations
Nasopharyngitis
Upper respiratory tract infection
Bronchitis
Urinary tract infection

Nervous system disorders
dizziness

Vascular disorders
hypertension

Skin and subcutaneous disorders
rash

Musculoskeletal and connective tissue disorders
Arthralgia
Back pain

Respiratory, thoracic, and mediastinal disorders
Cough

Gastrointestinal disorders
Diarrhoea

Occurrence of rash may be considered a hypersensitivity reaction with STRIVERDI® RESPIMAT®; as with all topical absorbed medication, other hypersensitivity reactions may develop.

Olodaterol is a member of the therapeutic class of long-acting beta$_2$-adrenergic agonists. Therefore, the occurrence of undesirable effects related to the beta-adrenergic agonist class should be taken into consideration, such as tachycardia, arrhythmia, palpitations, myocardial ischaemia, angina pectoris, hypertension or hypotension, tremor, headache, nervousness, insomnia, dizziness, dry mouth, nausea, muscle spasms, fatigue, malaise, hypokalemia, hyperglycaemia, and metabolic acidosis.

OVERDOSE

Symptoms
An overdose of olodaterol is likely to lead to exaggerated effects typical of beta$_2$-adrenergic agonists, i.e. myocardial ischaemia, hypertension or hypotension, tachycardia, arrhythmias, palpitation, dizziness, nervousness, insomnia, anxiety, headache, tremor, dry mouth, muscle spasms, nausea, fatigue, malaise, hypokalemia, hyperglycemia and metabolic acidosis.

Therapy
Treatment with STRIVERDI® RESPIMAT® should be discontinued. Supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardioselective beta-blockers may be considered, but only subject to extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Long-acting beta$_2$-adrenergic agonist, ATC code: R03AC19.

Mode of action
Olodaterol has a high affinity and high selectivity to the human beta$_2$-adrenoceptor.

In vitro studies have shown that olodaterol has more than 219-fold greater agonist activity at beta$_2$-adrenoceptors compared to beta$_1$-adrenoceptors and 1622-fold greater agonist activity compared to beta$_3$-adrenoceptors.

The compound exerts it´s pharmacological effects by binding and activation of beta$_2$-adrenoceptors after topical administration by inhalation.
Activation of these receptors in the airways results in a stimulation of intracellular adenyl cyclase, an enzyme that mediates the synthesis of cyclic-3',5' adenosine monophosphate (cAMP). Elevated levels of cAMP induce bronchodilation by relaxation of airway smooth muscle cells.
Olodaterol has the pre-clinical profile of a long-acting selective beta$_2$-adrenoceptor agonist (LABA) with a fast onset of action and a duration of action of at least 24 hours.

Beta-adrenoceptors are divided into three subtypes, $beta_1$-adrenoceptors predominantly expressed on cardiac smooth muscle, $beta_2$-adrenoceptors predominantly expressed on airway smooth muscle and $beta_3$-adrenoceptors predominantly expressed on adipose tissue. $Beta_2$-agonists cause bronchodilation. Although the $beta_2$-adrenoceptor is the predominant adrenergic receptor in the airway smooth muscle it is also present on the surface of a variety of other cells, including lung epithelial and endothelial cells and in the heart. The precise function of $beta_2$-receptors in the heart is not known, but their presence raises the possibility that even highly selective $beta_2$-adrenergic agonists may have cardiac effects.

Clinical Trials

Effects on cardiac electrophysiology

The effect of olodaterol on the QT/QTc interval of the ECG was investigated in 24 healthy male and female volunteers in a double-blind, randomised, placebo- and active (moxifloxacin) controlled study. Olodaterol at single doses of 10, 20, 30 and 50 microgram, demonstrated that compared with placebo, the mean changes from baseline in QT interval over 20 minutes to 2 hours after dosing increased dose-dependently from 1.6 (10 microgram olodaterol) to 6.5 ms (50 microgram olodaterol), with the upper limit of the two-sided 90% confidence intervals being less than 10 ms at all dose levels.
The effect of 5 microgram and 10 microgram STRIVERDI® RESPIMAT® on heart rate and rhythm was assessed using continuous 24-hour ECG recording (Holter monitoring) in a subset of 772 patients in the 48-week, placebo-controlled Phase 3 Trials. There were no dose- or time-related trends or patterns observed for the magnitudes of mean changes in heart rate or premature beats. Shifts from baseline to the end of treatment in premature beats did not indicate meaningful differences between olodaterol 5 microgram,10 microgram and placebo.

Clinical efficacy and safety

The Phase III clinical development program for STRIVERDI RESPIMAT included four pairs of replicate, randomised, double-blind, placebo-controlled trials in 3533 COPD patients (1281 received the 5 microgram dose, 1284 received the 10 microgram dose):
(i) two replicate, placebo-controlled, parallel group, 48 week trials (Trials 1 and 2)
(ii) two replicate, placebo- and active -controlled, parallel group, 48 week trials, with formoterol 12 microgram twice daily as active comparator (Trials 3 and 4)
(iii) two replicate, placebo- and active-controlled, 6 week cross-over trials, with formoterol 12 microgram twice daily as active comparator (Trials 5 and 6)
(iv) two replicate, placebo- and active-controlled, 6 week cross-over trials, with tiotropium HandiHaler 18 microgram once daily as active comparator (Trials 7 and 8).

All studies included lung function measurements (forced expiratory volume in one second, FEV_1); the 48 weeks studies evaluated peak (AUC_{0-3}) and trough lung function responses, while the 6 week studies evaluated the lung function profile over a continuous 24 hour dosing interval. The two replicate, placebo- and active-controlled, 48 week trials also included the Transition Dyspnoea Index (TDI) as a measure of dyspnoea and the St. George's Respiratory Questionnaire (SGRQ) as a measure of health-related quality of life.

Patients enrolled into the Phase III program were 40 years of age or older with a clinical diagnosis of COPD, had a smoking history of at least 10 pack years and had moderate to very severe pulmonary impairment (post-bronchodilator FEV_1 less than 80% predicted normal (GOLD Stage II-IV); post-bronchodilator FEV_1 to FVC ratio of less than 70%).

Patient characteristics

The majority of the 3104 patients recruited in the global, 48 week trials [Trials 1 and 2, Trials 3 and 4] were male (77%), white (66%) or Asian (32%), with a mean age of 64 years. Mean post-bronchodilator FEV_1 was 1.38 L (GOLD II [50%], GOLD III [40%], GOLD IV [10%]). Mean β_2-agonist responsiveness was 15% of baseline (0.160 L). With the exception of other long acting β_2-agonists, all pulmonary medications were allowed as concomitant therapy (e.g. tiotropium [24%], ipratropium [25%], inhaled steroids [45%], xanthines [16%]); patient enrolment was stratified by tiotropium use. In all four trials, the primary lung function efficacy endpoints were change from pre-treatment baseline in FEV_1 AUC_{0-3} and change from pre-treatment baseline in trough (pre-dose) FEV_1 (after 12 weeks in Trials 1 and 2; after 24 weeks in Trials 3 and 4).

The 6 week trials [Trials 5 and 6, Trials 7 and 8] were conducted in Europe and North America. In Trials 5 and 6, the majority of the 199 recruited patients were male (53%) and white (93%), with a mean age of 63 years. Mean post-bronchodilator FEV_1 was 1.43 L (GOLD II [54%], GOLD III [39%], GOLD IV [7%]). Mean β_2-agonist responsiveness was 17% of baseline (0.187 L). With the exception of other long acting β_2-agonists, all pulmonary medications were allowed as concomitant therapy (e.g. tiotropium [24%], ipratropium [16%], inhaled steroids [31%], xanthines [0.5%]). In Trials 7 and 8, the majority of the 230 recruited patients were male (69%) and white (99.6%), with a mean age of 62 years. Mean post-bronchodilator FEV_1 was 1.55 L (GOLD II [57%], GOLD III [35%], GOLD IV [7%]). Mean β_2-agonist responsiveness was 18% of baseline (0.203 L). With the exception of other long acting β_2-agonists and anti-cholinergics, all pulmonary medications were allowed as concomitant therapy (e.g. inhaled steroids [49%], xanthines [7%]).

Lung function

In the 48 week trials, STRIVERDI RESPIMAT, 5 microgram administered once daily in the morning, provided significant improvement ($p<0.0001$) in lung function within 5 minutes following the first dose (mean 0.130 L increase in FEV_1 compared with a pre-treatment baseline of 1.18 L). Significant improvement in lung function was maintained for 24 hours (mean 0.162 L increase in FEV_1 AUC_{0-3} compared to placebo, $p<0.0001$; mean 0.071 L increase in 24 hour trough FEV_1 compared to placebo, $p<0.0001$); the lung function improvements were evident in both tiotropium users and non-tiotropium users. The improvements in FEV_1 AUC_{0-3} and trough FEV_1 were comparable to twice daily formoterol. The bronchodilator effects of STRIVERDI RESPIMAT were maintained throughout the 48 week treatment period. STRIVERDI RESPIMAT also improved morning and evening PEFR (peak expiratory flow rate) as measured by patient's daily recordings compared to placebo.

In the 6 week trials, STRIVERDI RESPIMAT showed a significantly greater FEV_1 response compared to placebo ($p<0.0001$) over the full 24 hour dosing interval (Figure 1, Figure 2, Table 1).

Figure 1 **FEV_1 profile for STRIVERDI RESPIMAT 5 microgram and placebo over a continuous 24 hour dosing interval (Trials 5 and 6; combined dataset; anti-cholinergics allowed as concomitant medication)**

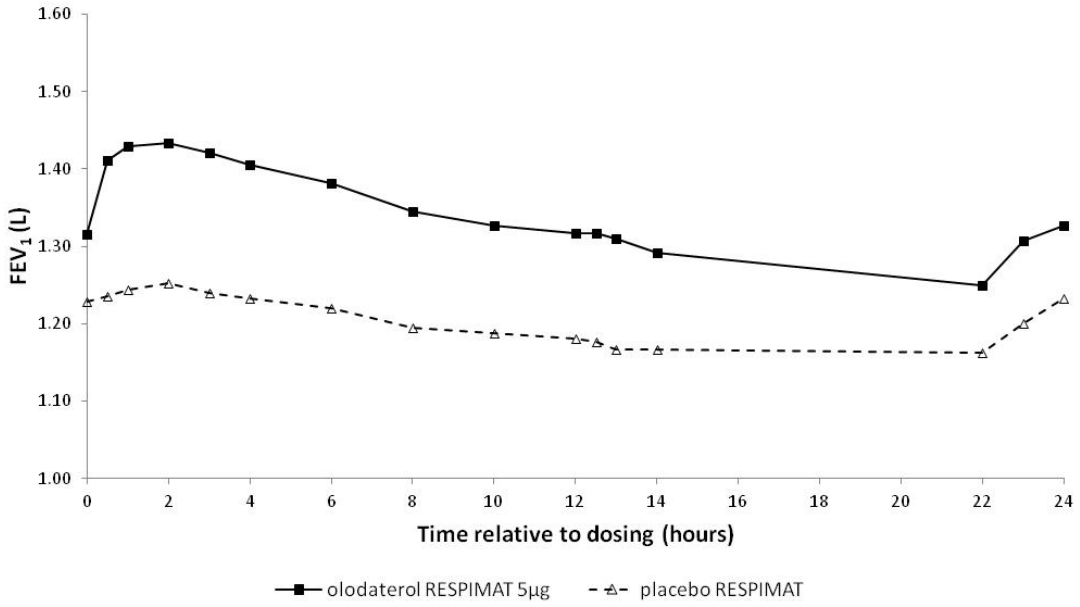


Figure 2 **FEV_1 profile for STRIVERDI RESPIMAT 5 microgram and placebo over a continuous 24 hour dosing interval (Trials 7 and 8; combined dataset; anti-cholinergics not allowed as concomitant medication)**

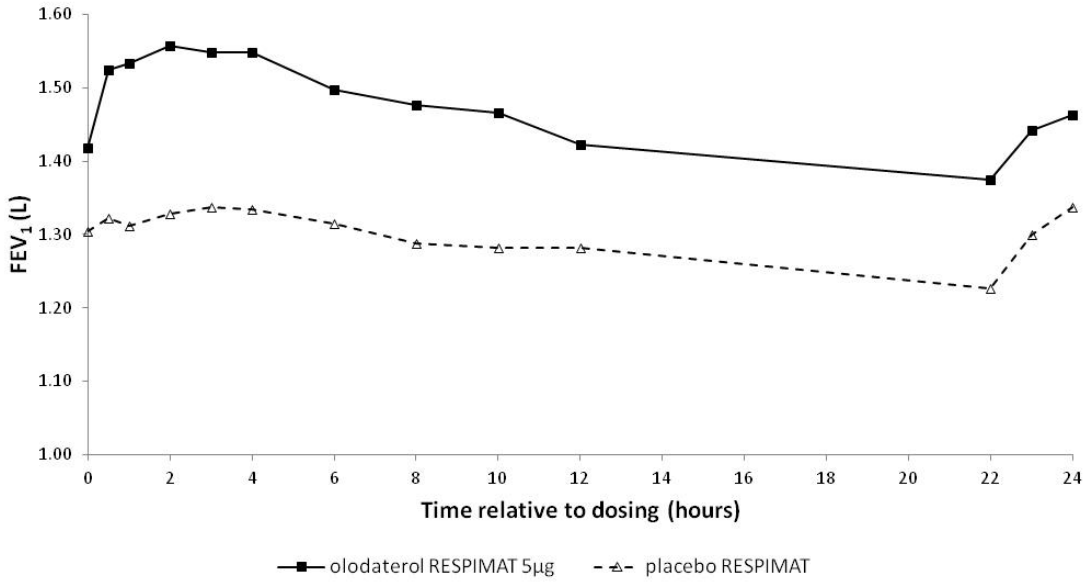


Table 1 **Differences in FEV_1 for STRIVERDI RESPIMAT 5 microgram compared to placebo over a continuous 24 hour dosing interval after 6 weeks treatment in Trials 5 and 6 (combined dataset) and Trials 7 and 8 (combined dataset)**

	FEV_1: difference vs. placebo (L)[1]			
	3 hr average	12 hr average	24 hr average	Trough
Trials 5 amd 6	0.175	0.160	0.137	0.102
Trials 7 and 8	0.211	0.193	0.168	0.134

pre-treatment baseline FEV_1 = 1.26 L (Trials 5 and 6) and 1.33 L (Trials 7 and 8)

Dyspnoea, Health-related Quality of Life, Rescue Medication Use, Patient Global Rating

The Transition Dyspnoea Index (TDI) and the St. George's Respiratory Questionnaire (SGRQ) were also included in the replicate, placebo- and active-controlled, 48 week trials [Trials 3 and 4]. After 24 weeks, there was no significant difference between STRIVERDI RESPIMAT, eformoterol and placebo in the TDI focal score (there was an unexpected improvement in the placebo group in one study) (Table 2).

Table 2 TDI focal score after 24 weeks of treatment

		Treatment Mean	Difference to Placebo Mean (p-value)
Primary analysis	Placebo	1.5 (0.2)	
	Olodaterol 5 µg once daily	1.9 (0.2)	0.3 (p=0.1704)
	Eformoterol 12 µg twice daily	1.8 (0.2)	0.2 (p=0.3718)

After 24 weeks, STRIVERDI RESPIMAT significantly improved mean SGRQ total score compared to placebo; improvements were seen in all 3 SGRQ domains (symptoms, activities, impact) as shown below in Table 3. More patients treated with STRIVERDI RESPIMAT had an improvement in SGRQ total score greater than the MCID (4 units) compared to placebo (50.2% vs. 36.4%), p<0.0001.

Table 3: SGRQ total and domain scores after 24 weeks of treatment

		Treatment Mean (change from baseline)	Difference to Placebo Mean (p-value)
Total score	Baseline	44.4	
	Placebo	41.6 (-2.8)	
	Olodaterol 5 µg once daily	38.8 (-5.6)	-2.8 (p=0.0034)
	Formoterol 12 µg twice daily	40.4 (-4.0)	-1.2 (p=0.2009)
Symptoms	Placebo	46.0	
	Olodaterol 5 µg once daily	41.1	-4.8 (p=0.0004)
	Formoterol 12 µg twice daily	43.7	-2.3 (p=0.0924)
Activities	Placebo	55.3	
	Olodaterol 5 µg once daily	52.9	-2.4 (p=0.0455)
	Formoterol 12 µg twice daily	55.0	-0.3 (p=0.7797)
Impact	Placebo	32.3	
	Olodaterol 5 µg once daily	29.7	-2.6 (p=0.0157)
	Formoterol 12 µg twice daily	30.8	-1.5 (p=0.1605)

Patients treated with STRIVERDI RESPIMAT used less daytime and nighttime rescue salbutamol compared to patients treated with placebo.

Exercise tolerance

The effect of STRIVERDI RESPIMAT on symptom-limited exercise tolerance in COPD patients was investigated in two replicate, randomised, double-blind, placebo-controlled, 6 week cross-over trials. In these trials, STRIVERDI RESPIMAT significantly improved exercise endurance time by 14.0% (p=0.0002) and 11.8% (p=0.0018) compared to placebo. STRIVERDI RESPIMAT also reduced lung hyperinflation (reduced

functional residual capacity, FRC), resulting in increased inspiratory capacity at rest and during exercise compared to placebo.

In each of the 48 week trials, patients treated with STRIVERDI RESPIMAT perceived a greater improvement in their respiratory condition compared to placebo, as measured by a Patient´s Global Rating (PGR) scale, providing further evidence of symptomatic benefit.

PHARMACOKINETICS

Information on the pharmacokinetics of olodaterol has been obtained from healthy subjects, COPD patients and asthma patients following oral inhalation of doses at and above the therapeutic dose.
Olodaterol showed linear pharmacokinetics with a dose-proportional increase of systemic exposure after single inhaled doses of 5 to 70 microgram and multiple once daily inhaled doses of 2 to 20 microgram.

On repeated once daily inhalation steady-state of olodaterol plasma concentrations was achieved after 8 days, and the extent of exposure was increased up to 1.8-fold as compared to a single dose.

Absorption
Olodaterol is rapidly absorbed, reaching maximum plasma concentrations generally within 10 to 20 minutes following drug inhalation. In healthy volunteers the absolute bioavailability of olodaterol following inhalation was estimated to be approximately 30%, whereas the absolute bioavailability was below 1% when given as an oral solution. Thus, the systemic availability of olodaterol after inhalation is mainly determined by lung absorption, while any swallowed portion of the dose only negligibly contributes to systemic exposure.

Distribution
Olodaterol exhibits multi-compartmental disposition kinetics after inhalation as well as after intravenous administration. The volume of distribution is high 1110 L, suggesting extensive distribution into tissue. *In vitro* binding of [^{14}C] olodaterol to human plasma proteins is independent of concentration and is approximately 60%.

Biotransformation
Olodaterol is substantially metabolized by direct glucuronidation and by O-demethylation at the methoxy moiety followed by conjugation. Of the six metabolites identified, only the unconjugated demethylation product (SOM 1522) binds to ß$_2$-receptors; this metabolite however is not detectable in plasma after chronic inhalation of the recommended therapeutic dose or doses of up to 4-fold higher.
Olodaterol thus is considered the only compound relevant for pharmacological action.

Cytochrome P450 isozymes CYP2C9 and CYP2C8, with negligible contribution of CYP3A4, are involved in the O-demethylation of olodaterol, while uridine diphosphate glycosyl transferase isoforms UGT2B7, UGT1A1, 1A7 and 1A9 were shown to be involved in the formation of olodaterol glucuronides.

Elimination

Total clearance of olodaterol in healthy volunteers is 872 mL/min, and renal clearance is 173 mL/min.
The terminal half-life following intravenous administration is 22 hours. The terminal half-life following inhalation in contrast is about 45 hours, indicating that the latter is determined by absorption rather than by elimination processes.

Following intravenous administration of [^{14}C]-labelled olodaterol, 38% of the radioactive dose was recovered in the urine and 53% was recovered in feces. The amount of unchanged olodaterol recovered in the urine after intravenous administration was 19%. Following oral administration, only 9% of the radioactivity was recovered in urine, while the major portion was recovered in feces (84%). More than 90% of the dose was excreted within 6 and 5 days following intravenous and oral administration, respectively. Following inhalation, excretion of unchanged olodaterol in urine within the dosing interval in healthy volunteers at steady state accounted for 5-7% of the dose.

Characteristics in Patients
A pharmacokinetic meta-analysis was performed utilizing data from 2 controlled clinical trials that included 405 patients with COPD and 296 patients with asthma who received treatment with STRIVERDI® RESPIMAT®.

The analysis showed that no dose adjustment is necessary based on the effect of age, gender and weight on systemic exposure in COPD patients after inhalation of STRIVERDI® RESPIMAT®.

Renal Insufficiency
In subjects with severe renal impairment (CL_{CR} <30 mL/min) [12] systemic exposure to olodaterol was on average 1.4-fold increased.
This magnitude of exposure increase does not raise any safety concerns given the safety experience of treatment with STRIVERDI® RESPIMAT® in clinical studies of up to one year at doses up to twice the recommended therapeutic dose.

Hepatic Insufficiency
In subjects with mild and moderate hepatic impairment systemic exposure to olodaterol was not affected. The effect of severe hepatic impairment on systemic exposure to olodaterol was not investigated.

Race
Comparison of pharmacokinetic data within and across studies revealed a trend for higher systemic exposure in Japanese and other Asians than in Caucasians.
No safety concerns were identified in clinical studies with Caucasians and Asians of up to one year with STRIVERDI® RESPIMAT® at doses up to twice the recommended therapeutic dose.

Drug-Drug Interactions
Drug-drug interaction studies were carried out using fluconazole as model inhibitor of CYP 2C9 and ketoconazole as potent P-gp and CYP inhibitor.

Fluconazole: Co-administration of 400 mg fluconazole once daily for 14 days had no relevant effect on systemic exposure to olodaterol.

Ketoconazole: Co-administration of 400 mg ketoconazole once daily for 14 days increased olodaterol Cmax by 66% and AUC0-1 by 68%.

Tiotropium: Co-administration of 5 microgram tiotropium bromide (delivered as fixed dose combination with 10 microgram olodaterol via the RESPIMAT) for 21 days had no relevant effect on systemic exposure to olodaterol, and vice versa.

TOXICOLOGY

Acute toxicity after single-dose inhalation, intravenous and oral - administration in mice and rats, was low.

The single-dose safety pharmacology studies showed the expected effects of a beta$_2$-adrenergic agonist including decrease of blood pressure, increase in heart rate and force of contraction.

The effects in the inhalation repeat-dose studies in mice, rats and dogs were mainly related to beta$_2$-adrenergic properties including increase in body weight and food consumption (rodents); increase in heart rate, changes in glycogen distribution in the liver, papillary muscle necrosis (dog).

In a inhalation repeat-dose study in juvenile dogs, doses of up 1046 microgram/kg/day were well tolerated. No signs of impairment of lung or heart development were present.
In the rat, no teratogenic effects occurred after inhalation of doses up to 1054 microgram/kg/day (approximately 1600 times the maximum recommended human daily inhalation dose (MRHDID) in adults (5 microgram) on a mg/m² basis). In pregnant NZW rabbits the administered inhalation dose of 2489 microgram/kg/day (exposure multiple versus the MRHDID of >3500 on AUC_{0-24}) of olodaterol exhibited fetal toxicity characteristically resulting from beta-adrenoceptor stimulation; these included patchy ossifications, short/bent bones, partially open eye, cleft palate, cardiovascular abnormalities. No significant effects occurred at an inhalation dose of 974 microgram/kg (approximately 1580 times the MRHDID in adults on a m² basis).

No impairment of male or female fertility or early embryonic development was seen in the rat up to inhalation doses of 3068 microgram/kg (approximately 3000 times the MRHDID in adults on a m² basis).

No effects were observed on mating, fertility or bearing of live implants to Day 14/15/16 of gestation in the F1 animals in the rat up to inhalation doses of 3665 microgram/kg/day (approximately 2970 times the MRHDID in adults on a m² basis).

In *in vivo* rat bone marrow micronucleus assay after inhalation exposure (up to approximately 2000 times the MRHDID in adults on a m² basis) and *in vitro* (Ames test, mouse lypmphoma assay) mutagenicity assays, olodaterol was free of any genotoxic potential up to very high dose levels. The increased frequency of micronuclei in rats at i.v. doses of at least 3500-times the MRHIDD was likely related to drug enhanced (compensatory) erythropoiesis. The mechanism for induction of micronuclei formation is likely not relevant at clinical exposures.

Inhalation carcinogenicity studies in mice and rats did not reveal any carcinogenic potential.

Lifetime treatment of rats induced class- and rodent-specific leiomyomas of the mesovarium at exposures approximately 2235-fold and 715-fold the exposure at the

dose of 5 microgram once-daily for humans (on systemic exposure). Lifetime treatment of mice induced class- and rodent-specific smooth muscle tumours (leiomyomas, leiomyosarcomas) of the uterus and incidences of sex cord stromal focal hyperplasia and luteal focal hyperplasia in the ovary at exposures approximately 477- to 3596-fold the exposure at the dose of 5 microgram once-daily for humans (on systemic exposure), again considered as class- and rodent specific (exposure multiples). Both studies revealed no evidence for an olodaterol-related human risk with regard to carcinogenicity or chronic toxicity.

Genotoxicity

There was no evidence for genotoxicity of olodaterol in standard assays *in vitro* (bacterial reverse mutation, mammalian forward mutation) and *in vivo* rat bone marrow micronucleus assay after inhalational doses up to 1,360 microgram/kg/day for 4 weeks (plasma AUC 1,100 times the anticipated clinical exposure). An increased frequency of micronuclei in rats after single intravenous doses of 10mg/kg or greater was likely related to drug enhanced (compensatory) erythropoiesis, and is unlikely to be relevant at clinical exposures.

Carcinogenicity

Lifetime treatment of rats induced class- and rodent-specific leiomyomas of the mesovarium at exposures approximately 213-fold the anticipated plasma AUC in adults at the dose of 5 microgram once daily. Lifetime treatment of mice induced class- and rodent-specific smooth muscle tumours (leiomyomas, leiomyosarcomas) of the uterus and incidences of sex cord stromal focal hyperplasia and luteal focal hyperplasia in the ovary at exposures approximately 40- to 400-fold the AUC in adults at the dose of 5 microgram once daily. These findings are not considered to indicate a carcinogenic hazard to patients.

AVAILABILITY

Solution for inhalation
1 RESPIMAT Reusable Inhaler and 1 cartridge Reg. No. DKI1552503275A1
1 Cartridge (single refill pack) Reg. No. DKI1552503275A1
One cartridge contains 4.0 ml providing 60 puffs (30 medicinal doses)

Only on doctor's prescription
Harus dengan resep dokter

Storage conditions:
Store below 30°C. Do not freeze.
Store in a safe place, out of the reach of children
Keep out of the sight and reach of children.

Shelf life : 3 years
Recommended use: 6 cartridges per inhaler
Exchange cartridge not later than 3 months after insertion.

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co. KG

Ingelheim am Rhein - Germany

For:
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

Imported by:
PT. Boehringer Ingelheim Indonesia
Bogor, Indonesia

Produk Informasi untuk Pasien

STRIVERDI® RESPIMAT®
OLODATEROL
2,5 mikrogram
Cairan Inhalasi

Bacalah seluruh leaflet ini dengan seksama sebelum anda mulai menggunakan obat ini karena leaflet ini berisikan informasi penting untuk anda.
- Simpanlah leaflet ini. Suatu saat Anda mungkin perlu membacanya kembali.
- Bila anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker anda.
- Obat ini diresepkan hanya untuk anda. Jangan berikan obat ini kepada orang lain. Hal ini dapat membahayakan mereka meskipun gejala penyakit mereka mirip dengan anda.
- Bila anda mengalami efek samping obat, bicarakan kepada dokter atau apoteker anda, termasuk efek samping obat yang tidak terdaftar dalam leaflet ini.

Apa saja yang terdapat dalam leaflet ini

1. Apakah STRIVERDI RESPIMAT dan digunakan untuk apa

STRIVERDI RESPIMAT membantu pasien yang mengalami penyakit paru obstruktif kronik (PPOK) agar dapat bernapas lebih mudah. Penyakit paru obstruktif kronik adalah penyakit paru jangka panjang yang menyebabkan sesak napas dan batuk. Istilah PPOK dikaitkan dengan kondisi bronkitis kronik dan emfisema. Penyakit paru obstruktif kronik merupakan penyakit jangka panjang oleh sebab itu anda sebaiknya menggunakan STRIVERDI RESPIMAT setiap hari dan tidak hanya ketika anda sedang mengalami masalah sesak napas atau gejala PPOK lainnya. Gejala PPOK meliputi nafas menjadi pendek, batuk, rasa tidak nyaman di dada dan batuk berdahak.

STRIVERDI RESPIMAT mengandung substansi aktif olodaterol yang merupakan bronkodilator kerja panjang yang dapat membantu membuka saluran napas anda sehingga memudahkan udara masuk dan keluar dari paru. Penggunaan STRIVERDI RESPIMAT secara teratur dapat juga membantu ketika anda sedang mengalami sesak napas yang terus menerus akibat penyakit ini dan akan membantu meminimalkan efek penyakit ini dalam keseharian anda.

Dosis yang tepat untuk STRIVERDI RESPIMAT dapat anda lihat pada bab 3. Bagaimana cara menggunakan STRIVERDI RESPIMAT dan instruksi penggunaannya tersedia pada bagian yang terpisah dari leaflet ini.

2. Apakah yang perlu anda ketahui sebelum anda menggunakan STRIVERDI RESPIMAT

Jangan gunakan Striverdi Respimat
Bila anda alergi (hipersensitif) terhadap olodaterol atau bahan lainnya yang terkandung dalam obat ini (terdaftar dalam bab 6)

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Peringatan dan perhatian
Bicarakan kepada dokter atau apoteker anda sebelum menggunakan STRIVERDI RESPIMAT
- Bila anda memiliki asma (anda sebaiknya tidak menggunakan STRIVERDI RESPIMAT untuk mengobati asma)
- Bila anda memiliki penyakit jantung
- Bila anda memiliki tekanan darah tinggi
- Bila anda memiliki epilepsi
- Bila anda memiliki masalah kelenjar tiroid spesifik yang disebut tirotoksikosis
- Bila anda memiliki diabetes
- Bila anda memiliki gangguan hati berat, karena STRIVERDI RESPIMAT belum diteliti pada populasi pasien ini.

Selama pengobatan dengan STRIVERDI RESPIMAT
- **Hentikan menggunakan obat dan beritahukan kepada dokter anda segera** bila anda mengalami rasa berat di dada, batuk, mengi atau sesak napas setelah menggunakan obat. Keadaan ini mungkin tanda dari suatu kondisi yang disebut bronkospasm.
- Bila napas anda terasa memberat atau bila anda mengalami ruam, bengkak atau gatal yang terjadi langsung setelah menggunakan inhaler anda, hentikan menggunakan obat ini dan beritahukan kepada dokter anda segera.
- Bila anda mengalami spasme otot, kelemahan otot atau irama jantung abnormal, konsultasi kepada dokter anda karena hal ini dapat saja disebabkan oleh rendahnya kadar natrium dalam darah

STRIVERDI RESPIMAT diindikasikan untuk pengobatan rumatan penyakit paru obstruktif kronik anda. **Obat ini tidak boleh digunakan untuk mengobati serangan sesak napas atau mengi yang terjadi secara tiba-tiba**.

Anak dan remaja
STRIVERDI RESPIMAT **tidak boleh** diberikan kepada **anak atau remaja (usia dibawah 18 tahun)**.

Obat lain dan STRIVERDI RESPIMAT
Beritahukan kepada dokter atau apoteker anda bila anda menggunakan atau akhir-akhir ini menggunakan obat-obatan lainnya.

Khususnya, beritahukan kepada dokter anda bila anda menggunakan:
- Obat-obatan untuk masalah pernapasan yang mirip dengan STRIVERDI RESPIMAT (agen β-adrenergik). Anda akan lebih cenderung untuk mengalami efek samping.
- Obat-obatan yang disebut beta bloker yang digunakan untuk tekanan darah tinggi atau masalah jantung lainnya (seperti propanolol) atau untuk masalah mata yang disebut glaukoma (seperti timolol). Obat-obat ini dapat menyebabkan hilangnya efek STRIVERDI RESPIMAT.
- Obat-obatan yang menurunkan jumlah natrium dalam darah anda, yaitu:
  - steroid (contohnya prednisolon),
  - diuretik (tablet penarik air),
  - obat-obatan untuk masalah pernapasan seperti teofilin.

  Bila anda menggunakan obat-obatan ini bersama dengan STRIVERDI RESPIMAT maka anda dapat mengalami gejala spasme otot, kelemahan otot atau irama jantung abnormal.
- Obat-obatan yang disebut antidepresan trisiklik atau penghambat MAO (seperti selegilin atau moklobemid), yang digunakan untuk mengobati gangguan neurologik atau psikiatrik seperti penyakit Parkinson atau depresi; menggunakan obat-obat ini akan meningkatkan kecenderungan terjadinya efek samping yang mempengaruhi jantung anda.

Hamil, menyusui dan fertilitas
Bila anda sedang hamil atau menyusui, berpikir bahwa anda mungkin hamil atau merencanakan untuk hamil, mintalah saran kepada dokter atau apoteker anda sebelum anda menggunakan obat ini.

Mengendarai dan mengoperasikan mesin
Bila anda merasa pusing ketika menggunakan Striverdi Respimat, jangan mengendarai atau mengoperasikan alat atau mesin.

3. Bagaimana cara menggunakan STRIVERDI RESPIMAT

Selalu gunakan obat ini tepat sesuai instruksi dokter anda. Anda sebaiknya mengecek kepada dokter atau apoteker anda bila anda tidak yakin.

STRIVERDI RESPIMAT hanya digunakan dengan cara inhalasi saja.

Dosis yang disarankan adalah:

STRIVERDI RESPIMAT efektif untuk 24 jam oleh karena itu anda hanya perlu menggunakan STRIVERDI RESPIMAT **SEKALI SEHARI**, bila memungkinkan gunakanlah pada waktu yang sama setiap harinya. Setiap kali anda menggunakannya, lakukan DUA SEMPROT.

PPOK adalah penyakit jangka panjang oleh sebab itu gunakan STRIVERDI RESPIMAT anda setiap hari dan tidak hanya ketika anda mengalami masalah pernapasan. Jangan menggunakan lebih dari dosis yang disarankan.

Pastikan anda mengetahui bagaimana menggunakan STRIVERDI RESPIMAT inhaler anda dengan tepat. Instruksi untuk cara menggunakan STRIVERDI RESPIMAT inhaler disediakan pada bagian lain dari leaflet ini.

Penggunaan pada anak dan remaja
Tidak ada kaitan menggunakan STRIVERDI RESPIMATpada populasi anak dan remaja (usia dibawah 18 tahun).

Bila anda menggunakan STRIVERDI RESPIMAT melebihi dari seharusnya
Anda memiliki risiko lebih tinggi untuk mengalami efek samping seperti nyeri dada, tekanan darah tinggi atau rendah, denyut jantung lebih cepat atau tidak teratur atau merasakan denyut jantung, pusing, gugup, sulit tidur, cemas, sakit kepala, gemetar, mulut kering, kram otot, mual, fatigue, malaise, kadar natrium rendah dalam darah (yang dapat menyebabkan gejala kram otot, lemah otot atau irama jantung abnormal), kadar gula darah tinggi, terlalu banyak asam dalam darah anda (yang dapat menyebabkan gejala mual, muntah, lemah, kram otot dan napas lebih cepat).

Bila anda lupa menggunakan STRIVERDI RESPIMAT
Bila anda terlupa menghisap satu dosis maka hisaplah satu dosis sesuai jadwal seharusnya pada hari berikutnya.
Jangan menggandakan dosis untuk menggantikan dosis yang terlupa.

Bila anda menghentikan menggunakan STRIVERDI RESPIMAT
Sebelum anda menghentikan menggunakan STRIVERDI RESPIMAT, anda sebaiknya berbicara dengan dokter atau apoteker anda. Bila anda menghentikan menggunakan STRIVERDI RESPIMAT maka tanda dan gejala PPOK dapat memberat.

Bila anda memiliki pertanyaan lebih lanjut mengenai cara menggunakan obat ini, tanyakan kepada dokter atau apoteker anda.

4. Kemungkinan efek samping

Sebagaimana semua obat lainnya, obat ini dapat menyebabkan efek samping meskipun tidak setiap orang mengalaminya.

Evaluasi efek samping berdasarkan frekuensi terjadinya:

Sering:	mempengaruhi 1 hingga 10 pasien dalam 100
Tidak sering:	mempengaruhi 1 hingga 10 pasien dalam 1.000
Jarang:	mempengaruhi 1 hingga 10 pasien dalam 10.000
Tidak diketahui:	frekuensi tidak dapat dihitung dari data yang tersedia

Berbagai efek samping yang diuraikan dibawah ini telah dialami oleh orang yang menggunakan obat ini dan mereka menyusunnya berdasarkan frekuensi yaitu sering, tidak sering, jarang atau tidak diketahui.

Tidak sering:
Nasofaringitis (pilek)
Pusing
Ruam

Jarang:
Artralgia

Tidak diketahui:
Hipertensi

Anda juga dapat mengalami efek samping yang diketahui terjadi pada obat-obatan untuk masalah pernapasan yang mirip dengan STRIVERDI RESPIMAT (agen beta adrenergik). Beberapa diantaranya adalah denyut jantung lebih cepat atau tidak teratur atau merasakan denyut jantung, nyeri dada, tekanan darah tinggi atau rendah, gemetar, sakit kepala, gugup, sulit tidur, pusing, mulut kering, mual, kram otot, fatigue, malaise, kadar natrium rendah dalam darah (yang dapat menyebabkan gejala spasme otot, lemah otot atau irama jantung abnormal), gula darah tinggi, terlalu banyak asam dalam darah anda (yang dapat menyebabkan gejala mual, muntah, lemah, kram otot dan napas lebih cepat).

Reaksi alergi segera seperti ruam, urtikaria, bengkak pada mulut dan wajah atau tiba-tiba sulit bernapas (edema angioneurotik) atau reaksi hipersensitivitas lainnya dapat terjadi setelah penggunaan STRIVERDI RESPIMAT. Bila hal ini terjadi, segera konsultasikan kepada dokter anda.

Disamping itu, seperti dengan obat-obatan inhalasi lainnya, beberapa pasien dapat mengalami rasa berat di dada yang tidak diduga, batuk, mengi atau sesak napas yang terjadi segera setelah inhalasi (bronkospasme).

Bila anda mengalami efek samping apapun, bicarakan dengan dokter atau apoteker anda, termasuk efek samping yang tidak terdaftar dalam leaflet ini.

5. Bagaimana cara menyimpan STRIVERDI RESPIMAT

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

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Jangan gunakan obat ini setelah tanggal kadaluarsa yang tertulis pada karton dan label inhaler. Tanggal kadaluarsa menunjukkan hari terakhir pada bulan tersebut. Respimat inhaler sebaiknya dibuang setelah 3 bulan sejak pertama kali digunakan (lihat Instruksi cara penggunaan pada halaman selanjutnya).

Jangan disimpan pada suhu beku.

Jangan buang obat apapun ke pembuangan air kotor atau pembuangan limbah rumah tangga. Tanyakan apoteker anda bagaimana cara membuang obat yang sudah tidak anda gunakan lagi. Sikap ini akan membantu melindungi lingkungan.

6. Isi paket dan informasi lainnya

Apakah kandungan yang terdapat dalam STRIVERDI RESPIMAT
Substansi aktifnya adalah olodaterol. Dosis pemberiannya adalah 2,5 mikrogram olodaterol per semprot (2 semprot adalah satu dosis obat) dan ekuivalen dengan 2,7 mikrogram olodaterol hidroklorida.
Dosis pemberian adalah dosis yang diterima oleh pasien setelah melewati *mouthpiece*.

Bahan lainnya adalah:
Benzalkonium klorida, disodium edetat, air purifikasi dan asam sitrat (anhidrosa)

Seperti apakah STRIVERDI RESPIMAT dan apakah isi paket

STRIVERDI RESPIMAT 2,5 mikrogram terdiri dari satu *cartridge* dengan cairan inhalasi dan satu Respimat inhaler. *Cartridge* harus dimasukkan kedalam inhaler sebelum pertama kali digunakan.

1 Respimat inhaler dan 1 *cartridge*, menyediakan 60 semprot (30 dosis obat)
Refill pack : 1 cartridge

Reg. No. DKI1552503275A1

Harus dengan resep dokter

Kondisi penyimpanan:
Simpan di bawah suhu 30°C. Jangan dibekukan
Simpan di tempat yang aman, jauh dari jangkaan anak-anak
Ganti *cartridge* dalam waktu tidak lebih dari 3 bulan setelah dimasukkan ke dalam alat.

Diproduksi oleh:
Boehringer Ingelheim Pharma GmbH & Co. KG
Ingelheim am Rhein, Jerman
Untuk:
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Jerman
Diimpor oleh:
PT. Boehringer Ingelheim Indonesia
Bogor, Indonesia

Instruksi Cara Penggunaan

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STRIVERDI® RESPIMAT®

Pendahuluan

STRIVERDI RESPIMAT (olodaterol). Bacalah Instruksi Cara Penggunaan ini sebelum Anda menggunakan STRIVERDI RESPIMAT *re-usable*.

Anda hanya perlu menggunakan inhaler ini SEKALI SEHARI. Setiap kali Anda menggunakannya, lakukan DUA SEMPROT.

Keterangan Gambar:

Inhaler	Alat Inhalasi
Cap	Penutup
Air vent	Lubang udara
Dose-release button	Tombol pelepas obat
Safety catch	Kunci pengaman
Clear base	Bagian dasar transparan
Cartridge	*Cartridge*
Cartridge *counter*	Penanda penggunaan *cartridge*
Piercing element	Bagian yang menonjol
Mouthpiece	Corong
Dose indicator	Indikator dosis
Front	Bagian depan
Back	Bagian belakang

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- Jika STRIVERDI RESPIMAT tidak digunakan selama lebih dari 7 hari, maka Anda sebaiknya melepaskan satu semprotan ke arah bawah.
- Jika STRIVERDI RESPIMAT tidak digunakan selama lebih dari 21 hari, maka Anda harus mengulangi langkah 4 hingga 6 dalam bagian *'Prepare for first Use'* hingga kabut terlihat kembali. Kemudian ulangi langkah 4 hingga 6 sebanyak tiga kali

Bagaimana cara merawat STRIVERDI RESPIMAT

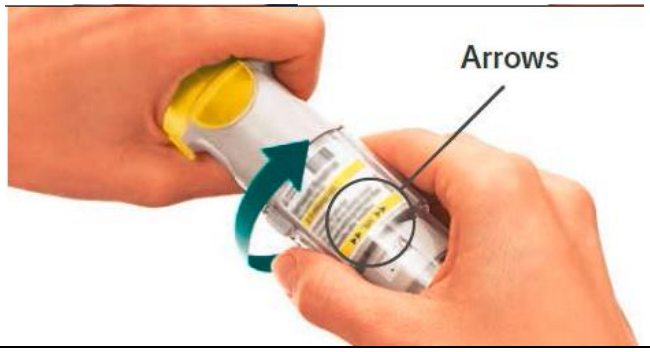
Bersihkan corong termasuk bagian logam dalam corong dengan lap atau tisu, paling sedikit sekali seminggu. Sedikit perubahan warna pada corong tidak mempengaruhi kinerja STRIVERDI RESPIMAT *re-usable* inhaler Anda. Jika diperlukan, bersihkan bagian luarnya menggunakan lap yang dibasahi.

Kapan dibutuhkan STRIVERDI RESPIMAT *re-usable* baru

Jika alat sudah digunakan sebanyak 6 kali, maka harus menggunakan STRIVERDI RESPIMAT *re-usable* (obat dan alat) baru.

Persiapan untuk Penggunaan Pertama Kali

1. Lepas bagian dasar transparan • Biarkan penutup tetap tertutup. • Tekan kunci pengaman sambil menarik bagian dasar yang transparan.	

2. Memasukkan *cartridge* • Dorong ujung *cartridge* yang kecil ke dalam inhaler. • Letakkan inhaler di atas permukaan yang keras dan dorong dengan kuat untuk memastikan *cartridge* telah masuk seluruhnya.	
3. Tandai penanda penggunaan *cartridge* dan masukkan kembali bagian dasar transparan • Tandai lingkarang yang tersedia pada label *cartridge* • Pasang kembali dasar transparan hingga terdengar bunyi klik.	
4. Putar • Pastikan penutup dalam posisi tertutup. • Putar bagian dasar sesuai arah panah yang terdapat pada label hingga terdengar bunyi klik (setengah putaran).	
5. Buka • Buka penutup hingga terbuka seluruhnya.	

6. Tekan • Arahkan inhaler ke bawah. • Tekan tombol pelepas obat. • Tutup penutup. • Ulangi langkah 4-6 hingga terlihat kabut. • **Setelah kabut terlihat**, kemudian ulangi langkah 4-6 sebanyak tiga kali. Sekarang alat inhalasi anda sudah siap digunakan untuk 60 semprot (30 dosis).	

Penggunaan Sehari-hari

PUTAR • Pastikan penutup dalam posisi tertutup. • **PUTAR** bagian dasar sesuai arah panah yang terdapat pada label hingga terdengar bunyi klik (setengah putaran).	
BUKA • **BUKA** penutup hingga terbuka seluruhnya.	

TEKAN • Buang napas dengan lambat dan dalam. • Katupkan bibir Anda pada ujung corong tetapi jangan menutup lubang udara. • Kemudian tarik napas dengan lambat dan dalam sambil **TEKAN** tombol pelepas obat dan teruskan menarik napas perlahan atau selama waktu yang nyaman untuk Anda. • Ulangi PUTAR, BUKA, TEKAN untuk total 2 semprot. • Tutup alat setalah selesai digunakan sampai anda menggunakannya kembali.	

Kapan harus mengganti *cartridge* STRIVERDI RESPIMAT

Indikator dosis menunjukkan berapa semprot yang masih tersedia dalam *cartridge*

	Sisa 60 semprot
	Kurang dari 10 semprot. Persiapkan *cartridge* baru.
	*Cartridge* anda sudah habis digunakan. Putar bagian transparan untuk dapat melepaskannya. Alat inhalasi anda sekarang dalam keadaan terkunci. Tarik *cartridge* dari alat inhalasi. Masukkan *cartridge* baru sampai terdengar bunyi 'klik' (lihat langkah 2). *Cartridge* baru akan lebih menempel daripada *cartridge* yang pertama kali digunakan (lanjutkan langkah 3). Ingatlah untuk selalu memasang kembali bagian dasar transparan supaya inhaler dalam posisi tidak terkunci.

Jawaban untuk Pertanyaan Umum

<u>Sangat sulit untuk memasukkan *cartridge* sampai masuk seluruhnya.</u>

Apakah Anda tidak sengaja memutar dasar transparan sebelum memasukkan *cartridge*? Buka penutup, tekan tombol pelepas obat, kemudianl masukkan *cartridge*.

Apakah Anda akan mengganti *cartridge*? *Cartridge* baru akan lebih melekat dibandingkan dengan cartridge yang pertama. Masukkan sampai terdengar bunyi *click*, kemudian lepaskan bagian dasar transparan.

Saya tidak dapat menekan tombol pelepas obat.

Apakah Anda sudah meletakkan dasar transparan ke tempat semula? Jika tidak, kembalikan dasar transparan untuk membuka inhaler. Respimat re-usable hanya berfungsi dengan dasar transparan kembali ke tempatnya.

Apakah Anda sudah memutar dasar transparan? Jika belum, putarlah dasar transparan secara berkelanjutan hingga terdengar bunyi klik (setengah putaran).

Apakah indikator dosis pada *cartridge* menunjukkan tanda panah putih dengan latar belakang merah? Obat telah habis. Silakan gunakan/masukkan *cartridge* baru Anda.

Sulit untuk melepaskan *cartridge* setelah habis digunakan

Tarik dan putar cartridge secara bersamaan.

Saya tidak dapat memutar dasar transparan.

Apakah bagian dasar transparan menjadi longgar dan indikator dosis pada *cartridge* menunjukkan tanda panah putih dengan latar belakang merah? Obat telah habis. Silakan gunakan/masukkan *cartridge* baru Anda.

Apakah sebelumnya Anda sudah memutar dasar yang transparan? Jika dasar transparan sudah diputar, silahkan ikuti langkah “BUKA” dan “TEKAN” pada bagian “Penggunaan Sehari-hari”.

Indikator dosis pada RESPIMAT *re-usable* menunjukkan posisi kosong terlalu cepat.

Apakah Anda menggunakan RESPIMAT *re-usable* seperti yang dianjurkan (dua semprot/sekali sehari)? RESPIMAT akan bertahan sampai 30 hari jika digunakan untuk dua semprot sekali sehari.

Apakah Anda terlalu sering menyemprotkan di udara untuk mengecek apakah RESPIMAT *re-usable* berfungsi? Begitu Anda menyiapkan RESPIMAT *re-usable*, tidak perlu lagi dilakukan tes penyemprotan untuk penggunaan sehari-hari.

Apakah Anda melepas dasar transparan beberapa kali? Jangan lepas dasar transparan sebelum *cartridge* habis. Setiap kali Anda melepas dasar transparan tanpa penggantian *cartridge*, penghitung dosis menghitung satu isapan dan dosis yang tersisa dapat berkurang.

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RESPIMAT *re-usable* saya tidak dapat menyemprot.

Apakah Anda sudah memasukkan *cartridge*? Jika belum, masukanlah *cartridge*. Ketika RESPIMAT *re-usable* siap digunakan, jangan lepaskan bagian dasar transparan sampai obat habis.

Apakah Anda mengulangi langkah Putar, Buka, Tekan kurang dari tiga kali setelah memasukkan *cartridge*? Ulangilah langkah Putar, Buka, Tekan sebanyak tiga kali setelah memasukkan *cartridge* seperti yang ditunjukkan pada langkah 4 sampai 6 pada bagian "Penggunaan Sehari-hari" .

Apakah indikator dosis pada *cartridge* menunjukkan tanda panah putih dengan latar belakang merah? Obat telah habis. Silakan gunakan/masukkan *cartridge* baru Anda.

RESPIMAT *re-usable* saya menyemprot secara otomatis.

Apakah penutup terbuka ketika Anda memutar dasar transparan? Tutuplah penutup, baru kemudian memutar dasar transparan.

Apakah Anda menekan tombol pelepas obat ketika memutar dasar transparan? Tutuplah penutup sehingga tombol pelepas obat terlindungi, kemudian putarlah dasar transparan.

Apakah Anda berhenti memutar dasar transparan sebelum terdengar bunyi klik? Putarlah dasar transparan secara berkelanjutan hingga terdengar bunyi klik (setengah putaran).

Apakah penutup terbuka pada saat Anda memasukkan *cartridge* baru? Tutup penutup, kemudian masukkan *cartridge* baru.

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