Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Striverdi Respimat 2.5 microgram inhalation solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The delivered dose is 2.5 microgram Olodaterol (as hydrochloride) per actuation.
The delivered dose is the dose which is available for the patient after passing the mouthpiece.

Excipient with known effect: This medicine contains 0.0011 mg benzalkonium chloride in each actuation.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation solution
Clear, colourless, inhalation solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Striverdi Respimat is indicated as a maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD).

4.2 Posology and method of administration

Posology
The medicinal product is intended for inhalation use only. The cartridge can only be inserted and used in the Respimat inhaler. Two actuations (puffs) from the Respimat inhaler comprise one medicinal dose.

Adults
The recommended dose is 5 microgram olodaterol given as two actuations (puffs) from the Respimat inhaler once daily, at the same time of the day.

The recommended dose should not be exceeded.

Elderly population
Elderly patients can use Striverdi Respimat at the recommended dose.

Hepatic impairment
Patients with mild and moderate hepatic impairment can use Striverdi Respimat at the recommended dose.

There are no data available for use of Striverdi Respimat in patients with severe hepatic impairment.

Renal impairment
Renally impaired patients can use Striverdi Respimat at the recommended dose. There is limited experience with the use of Striverdi Respimat in patients with severe renal impairment.

Paediatric population

There is no relevant use of Striverdi Respimat in the paediatric population (under 18 years).

Method of administration

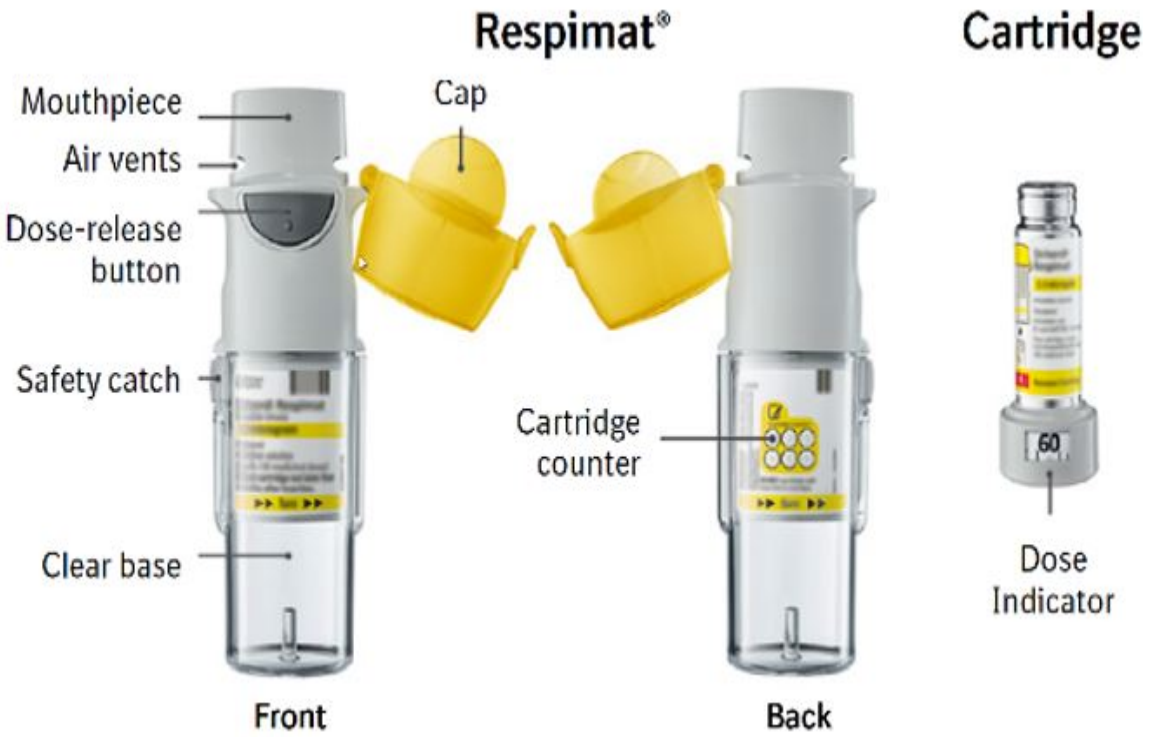
This medicinal product is intended for inhalation use only. The cartridge can only be inserted and used in the Respimat re-usable inhaler. Respimat is an inhaler device that generates a spray for inhalation. It is meant for use by a single patient and intended for multiple doses delivered by one cartridge.
The Respimat re-usable inhaler allows for replacement of the cartridge, and can be used with up to 6 cartridges.

Patients should read the instructions on how to use the Respimat re-usable inhaler before they start using Striverdi Respimat.

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

Instructions for handling and use of the Respimat re-usable inhaler

The patient will need to use this inhaler only ONCE A DAY. Each time used take TWO ACTUATIONS (PUFFS).



- If Striverdi Respimat has not been used for more than 7 days release one actuation (puff) towards the ground.
- If Striverdi Respimat has not been used for more than 21 days repeat steps 4 to 6 under 'Prepare for use' until a cloud is visible. Then repeat steps 4 to 6 three more times.

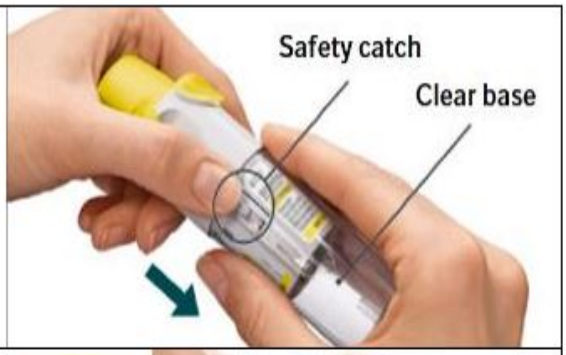
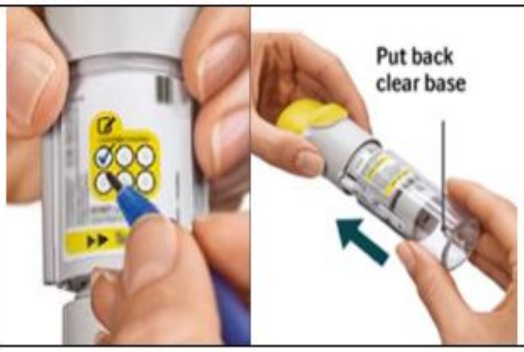
How to care for the Respimat re-usable inhaler

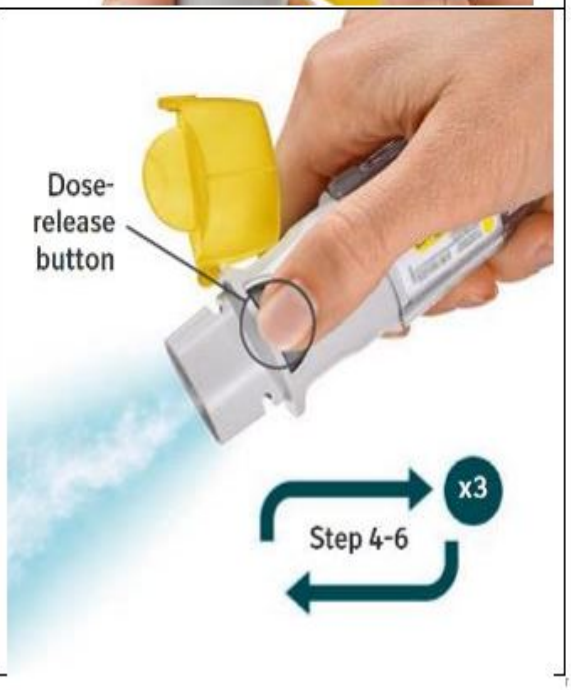
Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week.
Any minor discoloration in the mouthpiece does not affect the Respimat re-usable inhaler performance.
If necessary, wipe the outside of the Respimat re-usable inhaler with a damp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

When to replace the inhaler

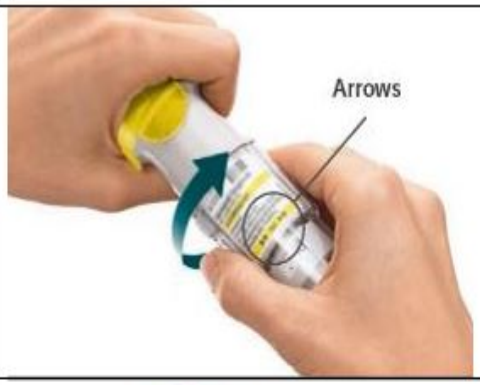
When the patient has used an inhaler with 6 cartridges, get a new Striverdi Respimat pack containing an inhaler.

Prepare for use

1. Remove clear base • Keep the cap closed. • Press the safety catch while pulling off the clear base with the other hand.	
2. Insert cartridge • Insert the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it clicks into place.	
3. Track cartridge and put the clear base back • 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. Turn • 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. The inhaler is now ready to use and will deliver 60 actuations (puffs) (30 doses).	

Daily use

TURN • Keep the cap closed. • **TURN** the clear base in the direction of the arrows on the label until it clicks (half a turn).	
OPEN • **OPEN** the cap until it snaps fully open.	
PRESS • Breathe out slowly and fully. • Close the lips around the mouthpiece without covering the air vents. Point the Inhaler to the back of the throat. • While taking a slow, deep breath through the mouth, **PRESS** the dose-release button and continue to breathe in slowly for as long as comfortable. • Hold the breath for 10 seconds or for as long as comfortable. • Repeat Turn, Open, Press for a total of 2 actuations (puffs). • Close the cap until the inhaler is used again.	

When to replace the Striverdi Respimat cartridge

The dose indicator shows how many actuations (puffs) remain in the cartridge.

60 actuations (puffs) remaining.

Less than 10 actuations (puffs) remaining. Obtain a new cartridge.

The cartridge is used up. Turn the clear base to loosen it. The 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.

4.3 Contraindications

Striverdi Respimat is contraindicated in patients with hypersensitivity to olodaterol or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Asthma
Striverdi Respimat should not be used in asthma. The long-term efficacy and safety of olodaterol in asthma have not been studied.

Acute bronchospasm
Striverdi Respimat, as a once daily maintenance bronchodilator should not be used 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.

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 ischaemic heart disease, severe cardiac decompensation, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, hypertension, and aneurysm, in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval (e.g. QT> 0.44 s), 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 4.5), which may increase the susceptibility to cardiac arrhythmias.

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

Anaesthesia
Caution needs to be taken in case of a planned operation with halogenated hydrocarbon anaesthetics due to an increased susceptibility to the adverse cardiac effects of beta agonist bronchodilators.

Excipients
Benzalkonium chloride may cause wheezing and breathing difficulties. Patients with asthma are at an increased risk for these adverse events.

Striverdi Respimat should not be used in conjunction with any other medications 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.

4.5 Interaction with other medicinal products and other forms of interaction

Adrenergic agents
Concomitant administration of other adrenergic agents (alone or as part of combination therapy) 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 hypokalemic effect of adrenergic agonists (see section 4.4).

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 and 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
No relevant effect on systemic exposure to olodaterol has been observed in drug-drug interaction studies with co-administration of fluconazole, used as model inhibitor of CYP2C9.

Co-administration of ketoconazole as potent P-gp and CYP inhibitor increased systemic exposure to olodaterol by approximately 70%. No dose adjustment is necessary.

Co-administration of olodaterol and tiotropium had no relevant effect on the systemic exposure to either of the two drugs.

In vitro investigations have shown that olodaterol does not inhibit CYP enzymes or drug transporters at the plasma concentrations achieved in clinical practice.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Striverdi Respimat in pregnant women available.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposures (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of Striverdi Respimat during pregnancy.

Like other beta$_2$-adrenergic agonists, olodaterol may inhibit labour due to a relaxant effect on uterine smooth muscle.

Breast-feeding
Clinical data from nursing women exposed to olodaterol are not available.It is unknown whether olodaterol/metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of olodaterol and/or its metabolites in milk.

Since the systemic exposure of the breast-feeding woman to olodaterol/metabolites is negligible at the human dose of 5 micrograms per day, relevant effects on the breastfed newborn/infant are not expected.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Striverdi Respimat therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Clinical data on fertility are not available for Striverdi Respimat. Preclinical studies performed with olodaterol showed no adverse effect on fertility.

4.7 Effects on ability to drive and use 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.

4.8 Undesirable effects

a. Summary of the safety profile
The most common adverse reactions at the recommended dose were nasopharyngitis, dizziness, hypertension, rash and arthralgia. These were usually mild or moderate in intensity.

b. Tabulated summary of adverse reactions
The frequencies assigned to the undesirable effects listed below are based on the crude incidence rates of adverse drug reactions (i.e. events attributed to olodaterol) observed in the olodaterol 5 microgram dose group (1035 patients), pooled from 6 placebo-controlled, parallel group clinical trials in COPD patients with treatment periods ranging between 4 and 48 weeks.

Frequency is defined using the following convention:

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), not known (cannot be estimated from the available data)

System Organ Class / MedDRA Preferred Term	**Frequency**
Infections and infestations	
Nasopharyngitis	Uncommon
Nervous system disorders	
Dizziness	Uncommon
Vascular disorders	
Hypertension	Rare
Skin and subcutaneous tissue disorders	
Rash	Uncommon
Musculoskeletal and connective tissue disorders	
Arthralgia	Rare

c. Description of selected adverse reactions
Occurrence of rash may be considered a hypersensitivity reaction with Striverdi Respimat; as with all topical absorbed medication, other hypersensitivity reactions may develop.

d. Beta$_2$- agonist adverse reaction profile
Striverdi Respimatis 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, hyperglycemia, and metabolic acidosis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA
Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms
An overdose of olodaterol is likely to lead to exaggerated effects typical of beta$_2$-adrenergic agonists, e.g. 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.

Treatment of overdose
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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases; Selective beta$_2$-adrenoreceptor agonists, ATC code: R03AC19

Mechanism of action
Olodaterol has a high affinity and high selectivity to the human beta$_2$-adrenoceptor.
In vitro studies have shown that olodaterol has 241-fold greater agonist activity at beta$_2$-adrenoceptors compared to beta$_1$-adrenoceptors and 2299-fold greater agonist activity compared to beta$_3$-adrenoceptors.
The compound exerts its 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.

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 for individually corrected QT (QTcI).

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- and active-controlled, parallel-group, 48-week trials, with formoterol 12 microgram twice daily as active comparator [Trials 1 and 2]

(ii) two replicate, placebo-controlled, parallel group, 48-week trials [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 Dyspnea Index (TDI) as a measure of dyspnea 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 24 weeks in Trials 1 and 2; after 12 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 magnitude of the bronchodilating effect of olodaterol (FEV_1 AUC_{0-3} response) was dependent on the degree of reversibility of airflow limitation at baseline (tested by administration of a short-acting beta-agonist bronchodilator); patients with a higher degree of reversibility at baseline generally exhibited a higher bronchodilator response with olodaterol than patients with a lower degree of reversibility at baseline. For both olodaterol and active comparator, the bronchodilatory effect (when measured in L) was lower in patients with more severe COPD. 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 (mean 0.175 L [Trials 5 and 6] and 0.211 L [Trials 7 and 8] increase in FEV_1 AUC_{0-3} compared to placebo, $p<0.0001$; mean 0.137 L [Trials 5 and 6] and 0.168 L [Trials 7 and 8] increase in FEV_1 AUC_{0-24} compared to placebo, $p<0.0001$).mean 0.102 L [Trials 5 and 6] and 0.134 L [Trials 7 and 8] increase in 24 hour trough FEV_1 compared to placebo, $p<0.0001$). Improvements in lung function were comparable to twice daily formoterol [Trials 5 and 6; mean 0.205 L increase in FEV_1 AUC_{0-3} compared to placebo; mean 0.108 L increase in 24 hour trough FEV_1 compared to placebo ($p<0.0001$)] and once daily tiotropium HandHaler [Trials 7 and 8; mean 0.211 L increase in FEV_1 AUC_{0-3} compared to placebo; mean 0.129 L increase in 24 hour trough FEV_1 compared to placebo ($p<0.0001$)].

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

The Transition Dyspnea Index (TDI) and the St. George's Respiratory Questionnaire (SGRQ) were also included in the replicate, placebo- and active-controlled, 48-week trials [Trials 1 and 2].

After 24 weeks, there was no significant difference between Striverdi Respimat, formoterol and placebo in the TDI focal score, due to an unexpected improvement in the placebo group in one study (Table 1); in a post-hoc analysis that accounted for patient discontinuations, the difference between Striverdi Respimat and placebo was significant.

Table1 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 micrograms once daily	1.9 (0.2)	0.3 (p=0.1704)
	Formoterol 12 micrograms twice daily	1.8 (0.2)	0.2 (p=0.3718)
Post-hoc analysis	Placebo	1.5 (0.2)	
	Olodaterol 5 micrograms once daily	2.0 (0.2)	0.5 (p=0.0270)
	Formoterol 12 micrograms twice daily	1.8 (0.2)	0.4 (p=0.1166)

After 24 weeks, Striverdi Respimat significantly improved mean SGRQ total score compared to placebo (Table 2); improvements were seen in all 3 SGRQ domains (symptoms, activities, impact). 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 2 SGRQ totalscores 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 micrograms once daily	38.8 (-5.6)	-2.8 (p=0.0034)
	Formoterol 12 micrograms twice daily	40.4 (-4.0)	-1.2 (p=0.2009)

Patients treated with Striverdi Respimat used less daytime and nighttime rescue salbutamol compared to patients treated with 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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Striverdi Respimat in all subsets of the paediatric population in chronic obstructive pulmonary disease (COPD) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

a. General Introduction

Information on the pharmacokinetics of olodaterol has been obtained from healthy subjects, COPD 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.

b. General Characteristics of the Active Substance after Administration of the Medicinal Product

Absorption

Olodaterol reaches 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.

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%.
Olodaterol is a substrate for the P-gp, OAT1, OAT3 and OCT1 transporter. Olodaterol is not a substrate for the following transporters: BCRP, MRP, OATP2, OATP8, OATP-B, OCT2 and OCT3.

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 binds to beta$_2$-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.

Following intravenous administration of [^{14}C]-labelled olodaterol, 38% of the radioactive dose was recovered in the urine and 53% was recovered in faeces. The amount of unchanged olodaterol recovered in the urine after intravenous administration was 19%. Following oral administration, only 9% of the radioactivity (0.7% unchanged olodaterol)was recovered in urine, while the major portion was recovered in faeces (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.

Olodaterol plasma concentrations after inhalation decline in a multiphasic manner with a terminal half-life of approximately 45 hours.

c. 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
There were no clinically relevant increases of systemic exposure in patients with renal impairment.

Hepatic Insufficiency
There was no evidence for differences in elimination of olodaterol, nor did protein binding differ, between subjects with mild or moderate hepatic impairment and their healthy controls. A study in subjects with severe hepatic impairment was not performed.

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.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans.
Increased incidences were observed of mesovarian leiomyoma in rats and of uterus leiomyoma and leiomyosarcoma in mice. This is considered a class effect which is observed in rodents after long-term exposure to high doses of β_2-agonists. Up to now, β_2-agonists have not been associated with cancer in humans.

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/m^2 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/day (approximately 1580 times the MRHDID in adults on a mg/m^2 basis).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate
Water, purified
Citric acid (anhydrous)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

In-use shelf life of the cartridge: 3 months

In-use shelf life of the inhaler: 1 year

Recommended use: 6 cartridges per inhaler

Note: The functioning of the RESPIMAT re-usable inhaler has been demonstrated in tests for 540 actuations (corresponding to 9 cartridges).

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Type and material of the container in contact with the medicinal product:
Solution filled into a polyethylene/polypropylene cartridge with a polypropylene cap with integrated silicone sealing ring. The cartridge is enclosed within an aluminium cylinder.
Each cartridge contains 4 ml inhalation solution

Pack sizes and devices supplied:

Single pack: 1 Respimat re-usable inhaler and 1 cartridge, providing 60 actuations (puffs) (30 medicinal doses)

Triple pack: 1 Respimat re-usable inhaler and 3 cartridges, providing 60 actuations (puffs) (30 medicinal doses) each

Single refill pack: 1 cartridge, providing 60 actuations (puffs) (30 medicinal doses)

Triple refill pack: 3 cartridges, providing 60 actuations (puffs) (30 medicinal doses) each

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

8 MARKETING AUTHORISATION NUMBER

PA0775/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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