STRIVERDI® RESPIMAT®

(olodaterol (as hydrochloride))

NAME OF THE MEDICINE

Active ingredient: Olodaterol (as olodaterol hydrochloride)

Chemical name: 2H-1,4-Benzoxazin-3H(4H)-one, 6-hydroxy-8-[(1R)-1-hydroxy-2-[[2-(4-methoxyphenyl)-1,1-dimethylethyl]amino]ethyl]-, monohydrochloride

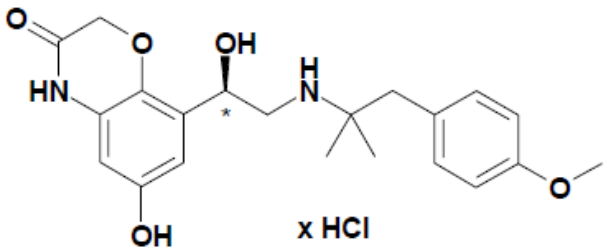
Molecular formula: Free base anhydrous: $C_{21}H_{26}N_2O_5$
Hydrochloride salt: $C_{21}H_{26}N_2O_5xHCl$

CAS number: 869477-96-3

Molecular weight: Free base anhydrous: 386.45
Hydrochloride salt: 422.91

Stereochemistry: (R) enantiomer

Structural formula:



DESCRIPTION

Olodaterol hydrochloride is a white to off-white powder. It is freely soluble in methanol, soluble in ethanol, sparingly soluble in acetone and slightly soluble in 2-propanol. Dissociation constants: pK_{a1} = 9.3; pK_{a2} = 10.1. Partition coefficient: Log P_{ow} (free base) = 3.0; Log D (pH 7.4) = 1.2.

STRIVERDI RESPIMAT is a soft mist inhaler delivering olodaterol solution for inhalation. The STRIVERDI RESPIMAT cartridge containing the solution for inhalation is only for use with the STRIVERDI RESPIMAT inhaler. The delivered dose is 2.5 microgram olodaterol per puff and is equivalent to 2.7 microgram olodaterol hydrochloride. Two puffs equal one dose of 5 micrograms. The delivered dose is the dose which is available for the patient after passing the mouthpiece.

Excipients include benzalkonium chloride, disodium edetate, citric acid - anhydrous and water - purified.

PHARMACOLOGY

Pharmacotherapeutic group: Long-acting $beta_2$-adrenergic agonist

Pharmacodynamics

Mechanism of action

Functional *in vitro* assays indicate greater activity of olodaterol at human $beta_2$-adrenoceptors than $beta_1$- or $beta_3$-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 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.

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.

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 (1,110 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%.

Metabolism

Olodaterol is substantially metabolised 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 significantly 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.

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 faeces. 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 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.

Pharmacokinetics in special patient groups

A pharmacokinetic meta-analysis was performed utilising 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), systemic exposure of olodaterol was on average 1.4-fold increased.

The magnitude of exposure increase dose 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 C_{max} by 66% and AUC_{0-1} 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.

CLINICAL TRIALS

The Phase III clinical development program for STRIVERDI RESPIMAT included four pairs of replicate, randomised, double-blind, placebo-controlled trials in 3,533 COPD patients (1,281 received the 5 microgram dose, 1,284 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 eformoterol 12 microgram twice daily as active comparator [Trials 3 and 4]

(iii) two replicate, placebo- and active-controlled, 6 week cross-over trials, with eformoterol 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 3,104 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 $beta_2$-agonist responsiveness was 15% of baseline (0.160 L). With the exception of other long acting $beta_2$-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 $beta_2$-agonist responsiveness was 17% of baseline (0.187 L). With the exception of other long acting $beta_2$-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 $beta_2$-agonist responsiveness was 18% of baseline (0.203 L). With the exception of other long acting $beta_2$-agonists and anticholinergics, all pulmonary medications were allowed as concomitant therapy (e.g. inhaled steroids [49%], xanthines [7%]).

Lung function

In the 48 week pivotal efficacy trials, STRIVERDI RESPIMAT 5 microgram administered once daily in the morning was shown to be statistically superior to placebo with respect to FEV_1 AUC (0-3hours) and trough FEV_1 (after 24 hours) at primary timepoints of 12 weeks and 24 weeks as shown below in Table1:

Table 1 Tabulated summary of efficacy: 48 week trials (olodaterol 5 µg once daily)

	Difference vs. Placebo [Mean, 95% CI]			
	FEV_1 AUC_{0-3} response (L)		**Trough FEV_1 response (L)**	
Trial	**12 wks (Day 85)**	**24 wks (Day 169)**	**12 wks (Day 85)**	**24 wks (Day 169)**
1222.11	**0.172 (0.135, 0.209)**	0.174 (0.136, 0.212)	**0.091 (0.054, 0.128)**	0.086 (0.049, 0.123)
1222.12	**0.151 (0.116, 0.185)**	0.165 (0.131, 0.200)	**0.047 (0.011, 0.084)**	0.069 (0.032, 0.106)
1222.13	0.178 (0.137, 0.219)	**0.151 (0.110, 0.193)**	0.083 (0.043, 0.123)	**0.078 (0.037, 0.118)**
1222.14	0.145 (0.108, 0.182)	**0.129 (0.091, 0.167)**	0.059 (0.022, 0.095)	**0.053 (0.015, 0.090)**
Average	0.162	0.155	0.070	0.072

Note: results for the primary endpoints are shown in bold
Common baseline mean (SE): 1222.11=1.139 (0.019); 1222.12=1.151 (0.020); 1222.13=1.204 (0.016); 1222.14=1.211 (0.015)

STRIVERDI RESPIMAT 5µg demonstrated a bronchodilatory effect at 5 minutes after the first dose with a mean increase in FEV_1 compared to placebo of 0.11 L (range 0.10 L to 0.12 L). The improvement in lung function was maintained for 24 hours.

In Trials 1 and 2, serial spirometric evaluations were also performed pre-dose and up to 12 hours in a subgroup of patients at 12 weeks of treatment. The mean change in FEV_1 AUC_{0-12h} compared to placebo was 0.137 L (95% CI 0.098, 0.177).

The improvement in lung function was evident in both tiotropium users and non-tiotropium users, although relatively lower effect was noted in tiotropium users in the replicate studies 11 and 12. The improvements in FEV_1 AUC_{0-3} and trough FEV_1 were comparable to twice daily eformoterol. The 10 microgram daily dose did not provide additional improvement compared to the 5 microgram daily dose. 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 2).

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; anticholinergics allowed as concomitant medication)

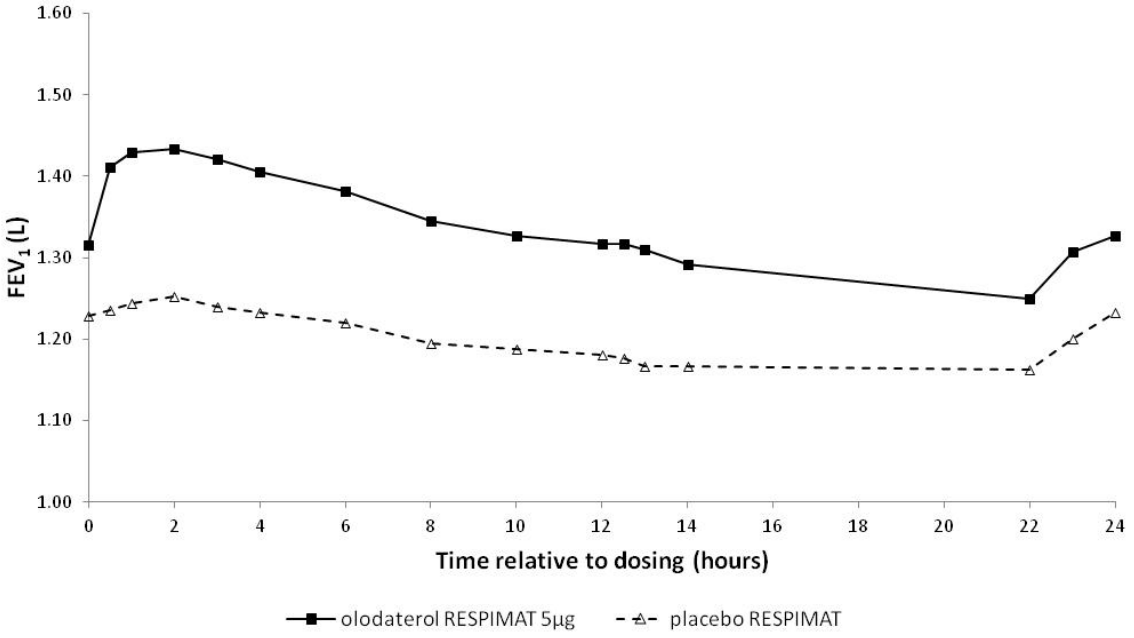


Figure 2 FEV_1 profile for STRIVERDI RESPIMAT 5 microgram and placebo over a continuous 24 hour dosing interval (Trials 7 and 8; combined dataset; anticholinergics not allowed as concomitant medication)

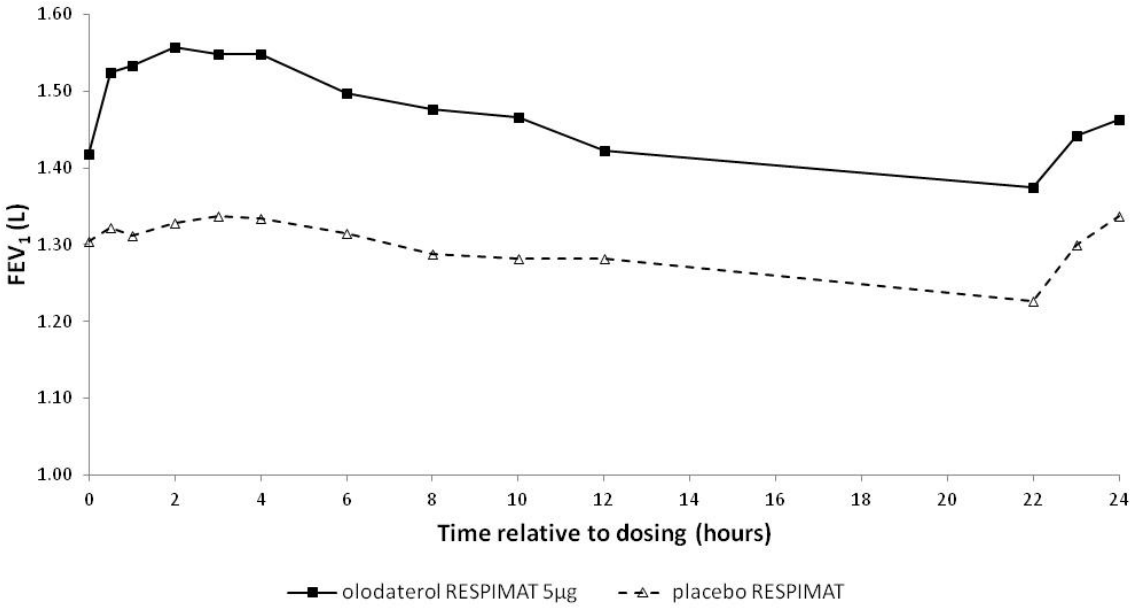


Table 2 Differences in FEV_1 for STRIVERDI RESPIMAT 5 microgram compared to placebo over a continuous 24 hour dosing interval after 6 weeks treatment in Trials 5 and 6 (combined dataset) and Trials 7 and 8 (combined dataset)

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

[1] 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 3).

Table 3 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 4. 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%).

Table 4 SGRQ total and domain scores after 24 weeks of treatment

		Treatment Mean (change from baseline)	Difference to Placebo Mean (95% CI)
Total score	Baseline	44.4	
	Placebo	41.6 (-2.8)	
	Olodaterol 5 µg once daily	38.8 (-5.6)	-2.8 (-4.751, -0.940)
	Eformoterol 12 µg twice daily	40.4 (-4.0)	-1.2 (−3.161, 0.665)
Symptoms	Placebo	46.0	
	Olodaterol 5 µg once daily	41.1	-4.8 (-7.516, -2.141)
	Eformoterol 12 µg twice daily	43.7	-2.3 (-5.025, 0.382)
Activities	Placebo	55.3	
	Olodaterol 5 µg once daily	52.9	-2.4 (-4.750, -0.048)
	Eformoterol 12 µg twice daily	55.0	-0.3 (-2.697, 2.023)
Impact	Placebo	32.3	
	Olodaterol 5 µg once daily	29.7	-2.6 (-4.658, -0.487)
	Eformoterol 12 µg twice daily	30.8	-1.5 (-3.594, 0.595)

Note: 4 units improvement (decrease) is considered a minimal clinically important treatment difference in SGRQ score.

Patients treated with STRIVERDI RESPIMAT used less daytime and night-time 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 had a statistically significantly improved exercise endurance time by 14.0% (mean difference of 52 seconds; p=0.0002) and 11.8% (mean difference of 42 seconds, 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.

INDICATIONS

STRIVERDI RESPIMAT is a long-acting beta$_2$-agonist indicated for once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

CONTRAINDICATIONS

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

PRECAUTIONS

Asthma

STRIVERDI RESPIMAT should not be used in asthma. The long-term efficacy 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.

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.

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 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, hospitalised 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 INTERACTIONS WITH OTHER MEDICINES), which may increase the susceptibility to cardiac arrhythmias.

Hyperglycaemia

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

Other

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.

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.

Effects on fertility

Clinical data on fertility are not available for STRIVERDI RESPIMAT. Nonclinical studies performed with olodaterol showed no adverse effect on fertility.

Decreased epididymal and testicular weights were seen in rats at inhalational doses greater than or equal to 55 microgram/kg/day; however there was no effect on sperm count, concentration or motility. 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 2,000 times the anticipated AUC in adults from a 5 microgram dose basis).

Use in pregnancy (Category B3)

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.

Olodaterol and/or its metabolites crossed the placenta in rats. In the rat, no teratogenic effects occurred after inhalation of doses up to 1,054 microgram/kg/day (plasma AUC more than 3,000 times the anticipated AUC in adults). In pregnant rabbits, the administered inhalational dose of 2,741 microgram/kg/day olodaterol exhibited fetal toxicity characteristic of beta-adrenoceptor stimulation; these included patchy ossifications, short/bent bones, partially open eye, cleft palate, and cardiovascular abnormalities. No significant effects occurred at an inhalational dose of 914 microgram/kg/day (approximately 1,300 times the anticipated AUC in adults).

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 fetus.

The inhibitory effect of beta-adrenergic agonists on uterine contraction should be taken into account.

Use in lactation

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

Olodaterol 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 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.

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.

INTERACTIONS WITH OTHER MEDICINES

In vitro studies indicated pharmacokinetic drug interactions involving CYP450 enzymes are not expected. Inhibitors of P-glycoprotein, OAT1, OAT3 or OCT1 may alter the systemic exposure to or disposition of olodaterol. Olodaterol was not an inhibitor of these transporters at clinically-relevant concentrations.

Adrenergic agents

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 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 and Tricyclic Antidepressants, QTc prolonging drugs

Monoamine 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 PHARMACOLOGY, 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.

ADVERSE EFFECTS

Adverse Events in Clinical Trials

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 3,104 COPD patients (77% males and 23% females) 40 years of age and older. Two of these trials were also active-comparator controlled. Of these patients, 876 and 883 patients were treated with STRIVERDI RESPIMAT 5 microgram and 10 microgram, respectively, taken with two actuations once daily. The olodaterol groups were composed of mostly Caucasians (66.4%) with a mean age of 64.3 years and a mean per cent predicted FEV_1 at baseline of 44% for both the 5 microgram and 10 microgram treatment groups. Control arms for comparison included placebo in all four trials plus eformoterol 12 microgram in two trials.

In the four pivotal clinical trials, 72% of patients exposed to any dose of STRIVERDI RESPIMAT reported an adverse event compared to 71% in the placebo group. The proportion of patients who discontinued due to an adverse event was 7.2% for STRIVERDI RESPIMAT treated patients compared to 8.8% for placebo treated patients. The adverse event most commonly leading to discontinuation was worsening COPD. The most common serious adverse events were COPD exacerbation, pneumonia, and atrial fibrillation.

Table 5 shows all adverse events that occurred with STRIVERDI RESPIMAT 5 microgram. The rates are derived from all reported adverse events of that type, regardless if considered drug-related or not by the clinical investigator.

Table 5 Number and frequency of adverse events greater than 2% (and higher than placebo) in COPD patients exposed to STRIVERDI RESPIMAT 5 microgram: Pooled data from 4 long-term (48 weeks), double-blind, active- and placebo-controlled clinical trials in COPD patients 40 years of age and older

Treatment	**STRIVERDI RESPIMAT 5 mcg once daily**	**Placebo**
System Organ Class **Adverse event**	**n = 876 n (%)**	**n = 885 n (%)**
Infections and infestations		
Nasopharyngitis	99 (11.3)	68 (7.7)
Upper respiratory tract infection	72 (8.2)	66 (7.5)
Bronchitis	41 (4.7)	32 (3.6)
Urinary tract infection	22 (2.5)	9 (1.0)
Respiratory, thoracic, and mediastinal disorders		
Cough	37 (4.2)	35 (4.0)
Nervous system disorders		
Dizziness	20 (2.3)	19 (2.1)
Skin and subcutaneous tissue disorders		
Rash*	19 (2.2)	10 (1.1)
Gastrointestinal disorders		
Diarrhoea	25 (2.9)	22 (2.5)
Musculoskeletal and connective tissue disorders		
Back pain	31 (3.5)	24 (2.7)
Arthralgia	18 (2.1)	7 (0.8)

*Rash includes a grouping of similar terms.

One additional adverse event is a recognised class effect and was reported in greater than 2% of patients (but not higher than placebo) exposed to STRIVERDI RESPIMAT 5 microgram:

Vascular disorders: Hypertension (3.1%)

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, hypokalaemia, hyperglycaemia, and metabolic acidosis.

DOSAGE AND ADMINISTRATION

STRIVERDI RESPIMAT is for oral inhalation only.

Adults

The recommended dose for adults is 5 microgram olodaterol given as two puffs from the STRIVERDI RESPIMAT inhaler once daily, at the same time of the day (see DOSAGE AND ADMINISTRATION, Instructions for Use and Handling).

Elderly

Elderly patients can use STRIVERDI RESPIMAT at the recommended dose.

Children

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

Patients with 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.

Patients with renal impairment

Renally impaired patients can use STRIVERDI RESPIMAT at the recommended dose.

Instructions for Use and Handling

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.

(See CONSUMER MEDICINE INFORMATION, Instructions for Use)

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

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, hypokalaemia, hyperglycaemia, and metabolic acidosis.

Treatment

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.

PRESENTATION AND STORAGE CONDITIONS

STRIVERDI RESPIMAT solution for inhalation is a clear, colourless solution contained in a plastic container crimped into an aluminium cylinder (cartridge) for use with the STRIVERDI RESPIMAT inhaler. The STRIVERDI RESPIMAT inhaler has a yellow-coloured cap. The STRIVERDI RESPIMAT cartridge is only intended for use with the STRIVERDI RESPIMAT inhaler.

STRIVERDI RESPIMAT is available in a labelled carton containing one STRIVERDI RESPIMAT cartridge of solution for inhalation and one STRIVERDI RESPIMAT inhaler delivering 60 metered puffs after preparation for use (equivalent to 30 doses when used as two puffs once daily). Each puff leaving the mouthpiece of the STRIVERDI RESPIMAT inhaler contains 2.5 microgram olodaterol, equivalent to 2.7 microgram olodaterol hydrochloride.

Storage conditions

Store below 30°C. Do not freeze.

STRIVERDI RESPIMAT should be used within 3 months after inserting the STRIVERDI RESPIMAT cartridge in the STRIVERDI RESPIMAT inhaler.

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

20 Nov 2013