PRODUCT MONOGRAPH

PrINSPIOLTO® RESPIMAT®

Tiotropium (as tiotropium bromide monohydrate) and Olodaterol (as olodaterol hydrochloride)
Inhalation Solution

2.5 mcg/2.5 mcg per actuation

INSPIOLTO® RESPIMAT® cartridge for use only with the INSPIOLTO® RESPIMAT® inhaler

Bronchodilator Combination
Long-Acting Muscarinic Antagonist (LAMA) and Long-Acting Beta$_2$-Adrenergic Agonist (LABA)

Boehringer Ingelheim (Canada) Ltd.
5180 South Service Road
Burlington, Ontario
L7L 5H4

www.boehringer-ingelheim.ca

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral inhalation	Inhalation Solution/ Each actuation delivers 2.5 mcg tiotropium (as tiotropium bromide monohydrate) and 2.5 mcg olodaterol (as olodaterol hydrochloride) from the mouthpiece.	Benzalkonium chloride, disodium edetate, purified water and hydrochloric acid.

INDICATIONS AND CLINICAL USE

INSPIOLTO RESPIMAT (tiotropium bromide monohydrate and olodaterol hydrochloride) is a combination of a long-acting muscarinic antagonist (LAMA) and a long-acting beta$_2$-adrenergic agonist (LABA) indicated for the long term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with Chronic Obstructive Pulmonary Disease (COPD), including chronic bronchitis and emphysema.

INSPIOLTO RESPIMAT is not indicated for the relief of acute deterioration of COPD.
INSPIOLTO RESPIMAT is not indicated for asthma use. The safety and effectiveness of INSPIOLTO RESPIMAT in asthma have not been established (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, General).

Geriatrics (> 65 years of age):
Elderly patients can use INSPIOLTO RESPIMAT at the recommended dose. No dosage adjustment is required.

Pediatrics (< 18 years of age):
INSPIOLTO RESPIMAT should not be used in patients under 18 years of age.

CONTRAINDICATIONS

INSPIOLTO RESPIMAT (tiotropium bromide monohydrate and olodaterol hydrochloride) is contraindicated in patients with hypersensitivity to tiotropium bromide monohydrate or olodaterol hydrochloride or to any of the excipients (see DOSAGE FORM COMPOSTION AND PACKAGING SECTION).

INSPIOLTO RESPIMAT is also contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, e.g. ipratropium.

All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication (see WARNINGS AND PRECAUTIONS). INSPIOLTO RESPIMAT is not indicated for the treatment of asthma.

WARNINGS AND PRECAUTIONS

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) to placebo added to patients' 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, one of the active ingredients in INSPIOLTO RESPIMAT.

INSPIOLTO RESPIMAT is only indicated for COPD. The safety and efficacy of INSPIOLTO RESPIMAT in patients with asthma have not been established. INSPIOLTO RESPIMAT is not indicated for the treatment of asthma.

General

INSPIOLTO RESPIMAT should not be used more frequently than once daily.

Not for use in asthma

INSPIOLTO RESPIMAT is only indicated for COPD. INSPIOLTO RESPIMAT should not be used in asthma due to the absence of long-term safety and efficacy data in asthma with INSPIOLTO RESPIMAT.

It has been shown that long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. Data from a 28-week, large placebo-controlled US study comparing the safety of a twice-daily long-acting beta$_2$-adrenergic agonist (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13 out of 13,176 in patients treated with salmeterol vs. 3 out of 13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma related death may represent a class effect of the long-

acting beta$_2$-adrenergic agonists, including olodaterol, one of the active ingredients of INSPIOLTO RESPIMAT. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with INSPIOLTO RESPIMAT has been conducted.

Acute bronchospasm

INSPIOLTO RESPIMAT is not indicated for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy. INSPIOLTO RESPIMAT has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist. INSPIOLTO RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of INSPIOLTO RESPIMAT in this setting is inappropriate.

When prescribing INSPIOLTO RESPIMAT, the healthcare professional should also provide the patient with an inhaled, short-acting bronchodilator for treatment of COPD symptoms that occur acutely, despite regular once-daily use of INSPIOLTO RESPIMAT.

When beginning treatment with INSPIOLTO RESPIMAT, patients who have been taking inhaled, short-acting bronchodilators on a regular basis (e.g. four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If INSPIOLTO RESPIMAT no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of INSPIOLTO RESPIMAT beyond the recommended dose is not appropriate in this situation.

Excessive Use and Use with other LABA and LAMA products

As with other inhaled bronchodilators, INSPIOLTO RESPIMAT should not be used more often or at higher doses than recommended. INSPIOLTO RESPIMAT should not be administered concomitantly with other medicines containing long-acting beta$_2$-adrenergic agonists, short- or long-acting muscarinic antagonists (e.g. ipratropium, tiotropium, glycopyrronium, aclidinium, umeclidinium), as an overdose may result (see DRUG INTERACTIONS).

Effects on Ability to Drive or Use Machines

There have been no studies investigating the effect of INSPIOLTO RESPIMAT on the ability to perform tasks that require judgement, motor or cognitive skills. The occurrence of dizziness or blurred vision may influence the ability to drive or to use machinery.

Anticholinergic Effects

Like other anticholinergic drugs, INSPIOLTO RESPIMAT should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Worsening of Narrow-Angle Glaucoma

INSPIOLTO RESPIMAT should be used with caution in patients with narrow-angle glaucoma. Patients should be cautioned to avoid getting the mist into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g. eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. Miotic drops alone are not considered to be effective treatment.

Worsening of Urinary Retention

INSPIOLTO RESPIMAT should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g. difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Cardiovascular

INSPIOLTO RESPIMAT is a combination of a long-acting beta$_2$-agonist (olodaterol) and a long-acting muscarinic antagonist (tiotropium). Cardiovascular effects, such as cardiac arrhythmias, e.g. atrial fibrillation and tachycardia, may be seen after the administration of sympathomimetic agents and muscarinic receptor antagonists, including INSPIOLTO RESPIMAT. In case such effects occur, treatment may need to be discontinued.

Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Cardiovascular effects such as tachycardia, arrhythmia, palpitations, myocardial ischemia, angina pectoris, hypertension or hypotension have been associated with use of beta-adrenergic agonists. In addition, beta-adrenergic agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Therefore, INSPIOLTO RESPIMAT, like all products containing beta-adrenergic agonists, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, acute myocardial infarction, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy and hypertension.

Heart Rate

Like other beta$_2$-agonists, olodaterol may produce clinically significant cardiovascular effects in some patients as measured by an increase in pulse rate, systolic or diastolic blood pressure, or cardiac arrhythmias such as atrial fibrillation, supraventricular tachycardia and extrasystoles. If such effects occur, INSPIOLTO RESPIMAT may need to be discontinued.

QTc Interval

As with other beta$_2$-agonists, caution is recommended if INSPIOLTO RESPIMAT is administered to patients with a known history of QTc prolongation, risk factors for torsade de pointes (e.g. hypokalemia), or patients who are taking medications known to prolong the QTc interval (see DRUG INTERACTIONS, Drugs known to prolong the QTc interval).

Hypokalemia
Beta$_2$-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). The decrease in serum potassium is usually transient, not requiring supplementation. INSPIOLTO RESPIMAT should be used with caution in patients predisposed to low levels of serum potassium. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment (see DRUG INTERACTIONS), which may increase the susceptibility to cardiac arrhythmias.

Clinically notable decreases in serum potassium were infrequent during clinical studies with long-term administration of INSPIOLTO RESPIMAT and with rates similar to either tiotropium or olodaterol.

Endocrine and Metabolism

Coexisting Conditions
INSPIOLTO RESPIMAT, like other medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-agonist salbutamol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hyperglycemia
Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with INSPIOLTO RESPIMAT plasma glucose should be monitored more closely in diabetic patients. INSPIOLTO RESPIMAT has not been investigated in patients whose diabetes mellitus is not controlled.

Respiratory

Benzalkonium Chloride
This medicine contains 0.0011 mg benzalkonium chloride in each actuation.

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

Paradoxical Bronchospasm
As with other inhaled medicines INSPIOLTO RESPIMAT may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, INSPIOLTO RESPIMAT should be discontinued immediately and alternative therapy substituted.

Hypersensitivity
As with all medications, immediate hypersensitivity reactions may occur after administration of INSPIOLTO RESPIMAT.

If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, INSPIOLTO RESPIMAT should be discontinued immediately and alternative therapy instituted. The patient should NOT be re-challenged with INSPIOLTO RESPIMAT (see CONTRAINDICATIONS).

Ophthalmologic

Worsening of Narrow-Angle Glaucoma (see WARNINGS AND PRECAUTIONS, Anticholinergic Effects).

Special Populations

Pregnant Women:
There is a limited amount of data from the use of tiotropium in pregnant women. For olodaterol no clinical data on exposed pregnancies are available.

Preclinical studies with tiotropium do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses.

Preclinical data for olodaterol revealed effects typical for beta-adrenergic agonists at high multiples of the therapeutic doses (see TOXICOLOGY).

INSPIOLTO RESPIMAT should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus. Women should be advised to contact their physician if they become pregnant while taking INSPIOLTO RESPIMAT.

Labour and delivery:
There are no adequate and well-controlled human studies that have investigated the effects of tiotropium and olodaterol, alone or in combination, during labour and delivery. Because beta-agonists may potentially interfere with uterine contractility, INSPIOLTO RESPIMAT should be used during labour only if the potential benefit justifies the potential risk.

Nursing Women:
Clinical data from nursing women exposed to tiotropium and/or olodaterol are not available.

In animal studies both tiotropium and olodaterol and/or its metabolites have been detected in the milk of lactating rats, but it is not known whether tiotropium and/or olodaterol passes into human breast milk. Therefore, the use of INSPIOLTO RESPIMAT by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

Fertility:
Clinical data on fertility are not available for tiotropium and olodaterol or the combination of both components. Animal studies performed with the individual components tiotropium and olodaterol showed no indication of any adverse effect on fertility (see TOXICOLOGY).

Pediatrics (< 18 years of age):
INSPIOLTO RESPIMAT should not be used in patients under 18 years of age. The safety and effectiveness of INSPIOLTO RESPIMAT in the pediatric population have not been established.

Geriatrics (> 65 years of age):
Based on available data, no adjustment of INSPIOLTO RESPIMAT dosage in geriatric patients is necessary.

Hepatic Insufficiency:
INSPIOLTO RESPIMAT contains olodaterol, which is predominantly metabolized in the liver. Patients with mild and moderate hepatic impairment can use INSPIOLTO RESPIMAT at the recommended dose.

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

Renal Insufficiency:
As with all predominantly renally excreted drugs, INSPIOLTO RESPIMAT should be used only if the expected benefit outweighs the potential risk in patients with moderate to severe renal impairment (creatinine clearance of < 50 ml/min). These patients should be monitored closely for potential adverse drug reactions (see ACTION and CLINICAL PHARAMACOLOGY).

Monitoring and Laboratory Tests
Beta$_2$-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment (see DRUG INTERACTIONS), which may increase the susceptibility to cardiac arrhythmias. It is therefore recommended that serum potassium levels be monitored in patients predisposed to low levels of serum potassium.

Due to the hyperglycemic effect observed with other beta-agonists, additional blood glucose monitoring is recommended in diabetic patients.

Worsening of Urinary Retention (see WARNING and PRECAUTIONS, Anticholinergic Effects).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Long-acting beta$_2$-adrenergic agonists such as olodaterol, one of the active ingredients of INSPIOLTO RESPIMAT, increase the risk of asthma-related death. INSPIOLTO RESPIMAT is not indicated for the treatment of asthma (see BOXED WARNING and WARNING AND PRECAUTIONS).

INSPIOLTO RESPIMAT is a combination of a long-acting muscarinic antagonist and a long-acting

beta$_2$-adrenergic agonist. Adverse reactions to INSPIOLTO RESPIMAT are expected to be similar in nature to reactions to other muscarinic antagonists and beta$_2$-agonists.

Adverse reactions to tiotropium are similar in nature to reactions to other anticholinergic bronchodilators and may include cardiovascular effects (atrial arrhythmias and tachycardia), ocular disorders (e.g. blurred vision), dysuria, urinary retention, gastrointestinal disorders (e.g. constipation and dry mouth), cough and immediate hypersensitivity reactions (urticaria, rash, bronchospasm, edema, angioedema, and anaphylactic shock or anaphylactic reaction). Many of the listed adverse reactions can be assigned to the anticholinergic properties of tiotropium bromide.

Adverse reactions that have been associated with other beta$_2$-adrenergic agonists include: tachycardia, arrhythmia, palpitations, myocardial ischaemia, angina pectoris, hypertension or hypotension, tremor, headache, nervousness, insomnia, dizziness, dry mouth, nausea, muscle spasms, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and immediate hypersensitivity reactions.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The clinical program for INSPIOLTO RESPIMAT included 7151 subjects with COPD in two 52-week active-controlled trials, one 12-week placebo-controlled trial, three 6-week placebo-controlled cross-over trials, and four additional trials of shorter duration. A total of 1988 subjects received at least 1 dose of INSPIOLTO RESPIMAT. Adverse reactions observed in the ≤12-week trials were consistent with those observed in the 52-week trials which formed the primary safety database.

The primary safety database consisted of pooled data from the two 52-week double-blind, active-controlled, parallel group confirmatory clinical trials. These trials included 5162 adult COPD patients (72.9% males and 27.1% females) 40 years of age and older. Of these patients, 1029 were treated with INSPIOLTO RESPIMAT once daily. The INSPIOLTO RESPIMAT group was composed of mostly Caucasians (71.1%) with a mean age of 63.8 years and a mean percent predicted FEV_1 at baseline of 43.2%. In these two trials tiotropium 5 mcg and olodaterol 5 mcg were included as active control arms and no placebo was used.

In these two clinical trials 74% of patients exposed to INSPIOLTO RESPIMAT reported an adverse reaction compared to 76.6% and 73.3% in the olodaterol 5 mcg and tiotropium 5 mcg groups, respectively. The proportion of patients who discontinued due to an adverse reaction was 7.4% for INSPIOLTO RESPIMAT treated patients compared to 9.9% and 9.0% for olodaterol 5 mcg and tiotropium 5 mcg treated patients. The adverse reaction most commonly leading to discontinuation was worsening COPD.

Table 1 shows all adverse reactions that occurred with an incidence of ≥1% in the INSPIOLTO RESPIMAT treatment group.

Table 1: Adverse drug reactions equal to or greater than (≥)1% in COPD patients exposed to INSPIOLTO RESPIMAT: Pooled data from the two 52-week, double-blind, active-controlled clinical trials in COPD patients 40 years of age and older

Treatment	INSPIOLTO RESPIMAT (once daily) n = 1029 n (%)	Tiotropium 5 mcg (once daily) n = 1033 n (%)	Olodaterol 5 mcg (once daily) n = 1038 n (%)
Body system (adverse drug reaction)			
Infections and infestations			
Nasopharyngitis	128 (12.4)	121 (11.7)	131 (12.6)
Upper respiratory tract infection	54 (5.2)	57 (5.5)	56 (5.4)
Bronchitis	31 (3.0)	23 (2.2)	33 (3.2)
Urinary tract infection	22 (2.1)	30 (2.9)	13 (1.3)
Sinusitis	21 (2.0)	13 (1.3)	18 (1.7)
Oropharyngeal candidiasis	11 (1.1)	4 (0.4)	10 (1.0)
Nervous system disorders			
Dizziness	18 (1.7)	16 (1.5)	14 (1.3)
Vascular disorders			
Hypertension	30 (2.9)	30 (2.9)	48 (4.6)
Respiratory, thoracic and mediastinal disorders			
Cough	40 (3.9)	45 (4.4)	31 (3.0)
Oropharyngeal pain	10 (1.0)	16 (1.5)	17 (1.6)
Dysphonia	10 (1.0)	11 (1.1)	9 (0.9)
Gastrointestinal disorders			
Diarrhea	24 (2.3)	27 (2.6)	33 (3.2)
Constipation	13 (1.3)	16 (1.5)	16 (1.5)
Dry mouth (usually mild)	16 (1.6)	19 (1.8)	10 (1.0)
General disorders and administration site conditions			
Edema peripheral	14 (1.4)	16 (1.5)	15 (1.4)
Fatigue	11 (1.1)	8 (0.8)	13 (1.3)
Musculoskeletal and connective tissue disorders			
Back pain	37 (3.6)	19 (1.8)	35 (3.4)
Arthralgia	18 (1.7)	13 (1.3)	14 (1.3)

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Infections and infestations: Lower respiratory tract infection

Metabolism and nutrition disorders: Dehydration

Nervous system disorders: Insomnia

Eye disorders: Intraocular pressure increased, Glaucoma, Vision blurred

Cardiac disorders: Palpitations, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Ventricular extrasystoles

Respiratory, thoracic and mediastinal disorders: Epistaxis, Pharyngitis, Laryngitis, Bronchospasm

Gastrointestinal disorders: Stomatitis, Gingivitis, Glossitis, Dysphagia, Gastroesophageal reflux disease, Intestinal obstruction including ileus paralytic

Skin and subcutaneous disorders: Rash, Pruritus, Urticaria, Skin infection, Skin ulcer, Dry skin, Hypersensitivity (including immediate reactions) and Angioedema

Musculoskeletal and connective tissue disorders: Joint swelling, Myalgia, Muscle spasms

Renal and urinary disorders: Urinary retention (usually in men with predisposing factors), Dysuria

General disorders and administration site conditions: Asthenia

Investigations: Electrocardiogram QT prolonged

Many of the listed undesirable effects can be assigned to either the anticholinergic properties of tiotropium or to the ß-adrenergic properties of olodaterol, the components of INSPIOLTO RESPIMAT.

Post-Market Adverse Drug Reactions

Currently, there is no evidence from post-market data for additional adverse drug reactions for INSPIOLTO RESPIMAT beyond those listed in the Clinical Trial Adverse Drug Reactions section.

The following adverse reactions have been identified during the worldwide use of SPIRIVA® RESPIMAT® and another tiotropium formulation, SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) Capsules for Oral Inhalation: Eye disorders: glaucoma, intraocular pressure increased, vision blurred; Cardiac disorder: atrial fibrillation, tachycardia, supraventricular tachycardia; Respiratory disorders: bronchospasm; Gastrointestinal disorders: glossitis, stomatitis; Metabolism and nutrition disorders: dehydration; Nervous system disorders: insomnia; Skin and immune system disorders: hypersensitivity (including immediate reactions), urticaria. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

Drug-Drug Interactions

Drug-drug interaction studies have been conducted with the mono components olodaterol and tiotropium. No specific drug-interaction studies were conducted for INSPIOLTO RESPIMAT.

Tiotropium is mainly excreted renally (approximately 74% of the intravenously administered dose). The remaining dose is mainly nonenzymatically cleared with a minor portion (<20% of intravenous dose) being metabolized by CYP2D6 and CYP3A4 (see METABOLISM). Tiotropium does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 even in supratherapeutic concentrations, which makes clinically relevant metabolic interactions with tiotropium unlikely.

Although no formal drug interaction studies have been performed, in clinical studies, INSPIOLTO RESPIMAT has been used concomitantly with other drugs commonly used to treat COPD including short-acting beta-adrenergic agonists, methylxanthines, and oral and inhaled corticosteroids. No safety findings were observed to contraindicate administration of these agents with INSPIOLTO RESPIMAT.

The chronic co-administration of tiotropium bromide with other anticholinergic-containing drugs has not been studied. Therefore, the chronic co-administration of other anticholinergic drugs with INSPIOLTO RESPIMAT is not recommended.

Drugs known to prolong QTc interval
INSPIOLTO RESPIMAT, as other $beta_2$-adrenergic agonist-containing drugs, should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Drugs known to prolong the QT-interval may increase the risk of ventricular arrhythmia (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Sympathomimetic Agents
Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of INSPIOLTO RESPIMAT (see WARNINGS AND PRECAUTIONS).

Treatments leading to Hypokalemia
$Beta_2$-adrenoceptor agonists have been associated with reductions in serum potassium levels. Concomitant treatment with xanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate any hypokalemic effect of adrenergic agonists (see WARNINGS AND PRECAUTIONS, Hypokalemia).

Beta- adrenergic Blockers
Beta-adrenergic blockers may weaken or antagonise the effect of olodaterol. Therefore, INSPIOLTO RESPIMAT should not be given together with beta-adrenergic blockers (including eye-drops) unless

there are compelling reasons for their use. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

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

Drug-Drug Interactions
Drug-drug interaction studies with olodaterol were carried out using fluconazole as model inhibitor of CYP 2C9 and ketoconazole as a strong P-gp and CYP3A inhibitor.

Table 2: Established or Potential Drug-Drug Interactions

Drug	Ref	Effect	Clinical comment
Fluconazole (inhibitor of CYP 2C9)	CT	Co-administration of 400 mg fluconazole once daily for 14 days had no relevant effect on systemic exposure to olodaterol.	No dose adjustment is necessary.
Ketoconazole (P-gp and CYP inhibitor)	CT	Co-administration of 400 mg ketoconazole once daily for 14 days increased olodaterol C_{max} by 66% and AUC_{0-1} by 68%.	No dose adjustment is necessary. Caution may be warranted with concomitant therapy.
P-gp Inhibitors	T	Co-administration may lead to increased olodaterol C_{max} and AUC_{0-1}.	No dose adjustment is necessary. Caution may be warranted with concomitant therapy.
Legend: CT = Clinical Trial; T = Theoretical			

Drug-Food Interactions

No food interaction study was conducted because any possible food effects on olodaterol and tiotropium systemic exposure are considered to be of no relevance for efficacy, tolerability and safety.

Drug-Lifestyle Interactions

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

However, patients should be advised that dizziness and blurred vision have been reported with the use of INSPIOLTO RESPIMAT. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience such symptoms, they should avoid potentially hazardous tasks such as driving or operating machinery.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Counselling by doctors on smoking cessation should be the first step in treating patients with COPD who smoke, independent of the clinical presentation i.e. chronic bronchitis (with or without airflow limitation) or emphysema. Cessation of smoking produces dramatic symptomatic benefits and has been shown to confer a survival advantage.

- As with other inhaled drugs containing beta$_2$-adrenergic agents, INSPIOLTO RESPIMAT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing a long-acting beta-adrenergic agonist or a long-acting muscarinic antagonist, as an overdose may result.

- When beginning treatment with INSPIOLTO RESPIMAT, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g. 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

- Patients should be made aware that for optimum benefit, INSPIOLTO RESPIMAT must be used regularly, even when asymptomatic.

Recommended Dose and Dosage Adjustment

The recommended dose for adults is 5 mcg tiotropium and 5 mcg olodaterol given as two inhalations from the RESPIMAT inhaler once daily, at the same time of the day.

The delivered dose is 2.5 mcg tiotropium and 2.5 mcg olodaterol per inhalation (2 inhalations comprise one medicinal dose).

Dosing in Special Populations

No dosage adjustment is required in patients over 65 years of age, patients with mild and moderate hepatic impairment, or renally impaired patients. However, as with all predominantly renally excreted drugs, INSPIOLTO RESPIMAT use should be monitored closely in patients with moderate to severe renal impairment.

INSPIOLTO RESPIMAT has not been studied in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY).

INSPIOLTO RESPIMAT should not be used in patients under 18 years of age.

Missed Dose

Patients should be advised that if they forget to take a dose, they should take one as soon as they remember. INSPIOLTO RESPIMAT should not be taken more than once per day (two inhalations/dose).

Administration

INSPIOLTO RESPIMAT should be administered once daily, at the same time of day, every day via inhalation through the RESPIMAT inhalation device only. To ensure proper administration of INSPIOLTO RESPIMAT, the doctor or other qualified health care professional should teach the patient how to operate the RESPIMAT inhalation device (see Part III CONSUMER INFORMATION).

OVERDOSAGE

Symptoms

Tiotropium:
High doses of tiotropium bromide may lead to signs and symptoms of exaggerated anticholinergic effects, such as constipation, voiding difficulties or increased intraocular pressure causing pain, vision disturbances or reddening of the eye.

No adverse events, beyond dry mouth/throat and dry nasal mucosa in a dose-dependent (10-40 mcg daily) incidence, were observed following 14-day dosing of up to 40 mcg tiotropium inhalation solution in healthy subjects with the exception of pronounced reduction in salivary flow from day 7 onwards.

Should signs of serious anticholinergic toxicity appear, vital signs should be carefully monitored and appropriate therapy should be initiated.

Olodaterol:
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, QTc prolongation, 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 INSPIOLTO RESPIMAT should be discontinued. Supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Electrocardiogram monitoring is recommended in the event of overdosage. 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Tiotropium:
Tiotropium is a long acting muscarinic receptor antagonist (LAMA), also known as an anticholinergic. It has a similar affinity to the subtypes of muscarinic receptors M_1 to M_5. In the lungs, inhibition of M_3-receptors at the smooth muscle results in relaxation of the airways. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. Tiotropium bromide is a quaternary ammonium molecule with duration of action sufficient to provide 24 hours of bronchoprotection with once-a-day inhalational administration.

The long duration of action of tiotropium is thought to be due to its slow dissociation kinetics from the muscarinic M_3-receptor subtype. Dissociation from M_2-receptors is faster than from M_3, which in functional in vitro studies, elicited (kinetically controlled) receptor subtype selectivity of M_3 over M_2. As an N-quaternary anticholinergic, tiotropium is topically selective when administered by inhalation to the lung. Pharmacological *in vitro* and *in vivo* studies profiled tiotropium as a potent, long acting bronchodilator suitable for a once-daily dose regimen.

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

In vitro studies have shown that olodaterol has more than 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.

Pharmacodynamics

Tiotropium

Primary Pharmacodynamic Effects

The primary pharmacodynamic effect in subjects with COPD following inhalation of tiotropium is bronchodilation, which is primarily a site-specific, rather than a systemic effect. Tiotropium bromide, administered once daily in the COPD population, provided significant improvement in lung function (forced expiratory volume in one second, FEV_1 and forced vital capacity, FVC) within 30 minutes following the first dose which was maintained for 24 hours. Pharmacodynamic steady state was reached within one week with the majority of bronchodilation observed by the third day. Repeated inhalation of SPIRIVA RESPIMAT has not been linked with tolerance towards the bronchodilatory effects of the drug. Bronchodilatory effects gradually returned to baseline levels upon cessation of treatment with no evidence of rebound.

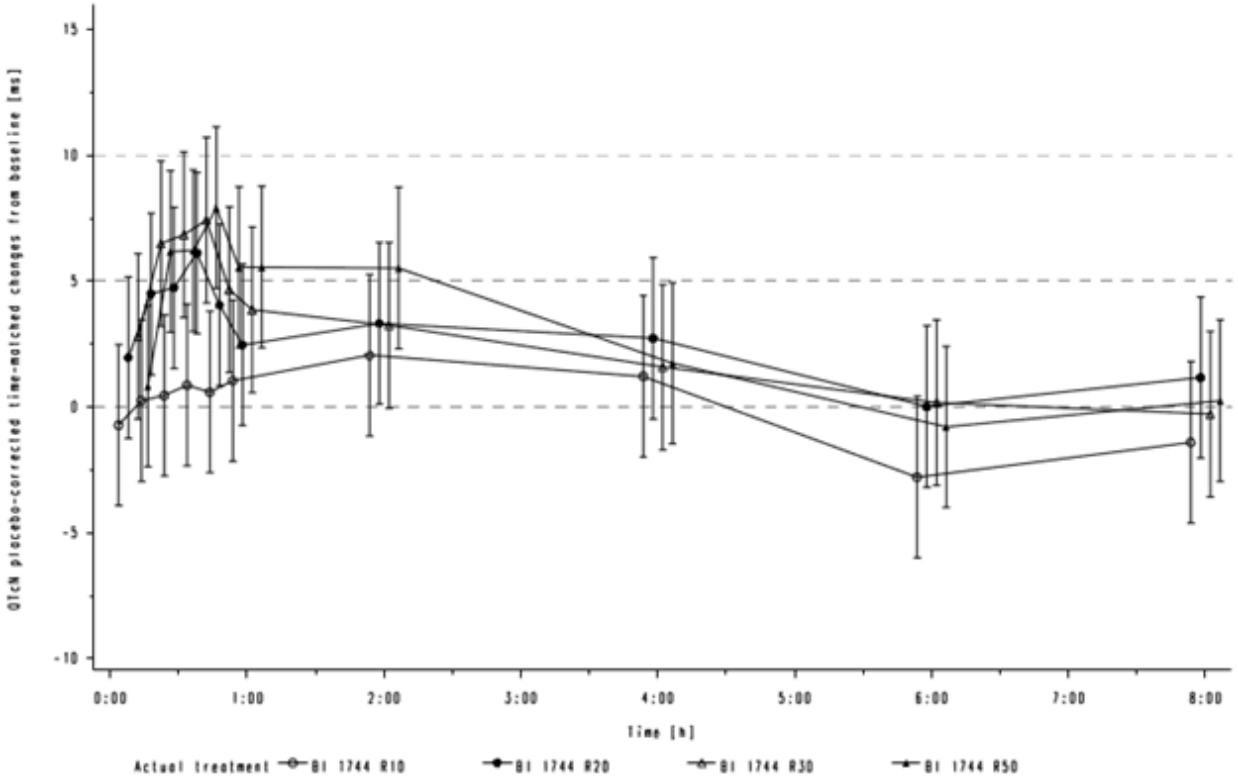
Secondary Pharmacodynamic Effects

Cardiac Electrophysiology:
In a multicenter, randomized, double-blind trial using tiotropium dry powder for inhalation that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30 to 60 msec was higher in the tiotropium group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs., 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical trials with tiotropium did not detect an effect of the drug on QTc intervals.

The effect of tiotropium dry powder for inhalation on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received tiotropium inhalation powder 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for tiotropium inhalation powder 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥60 msec.

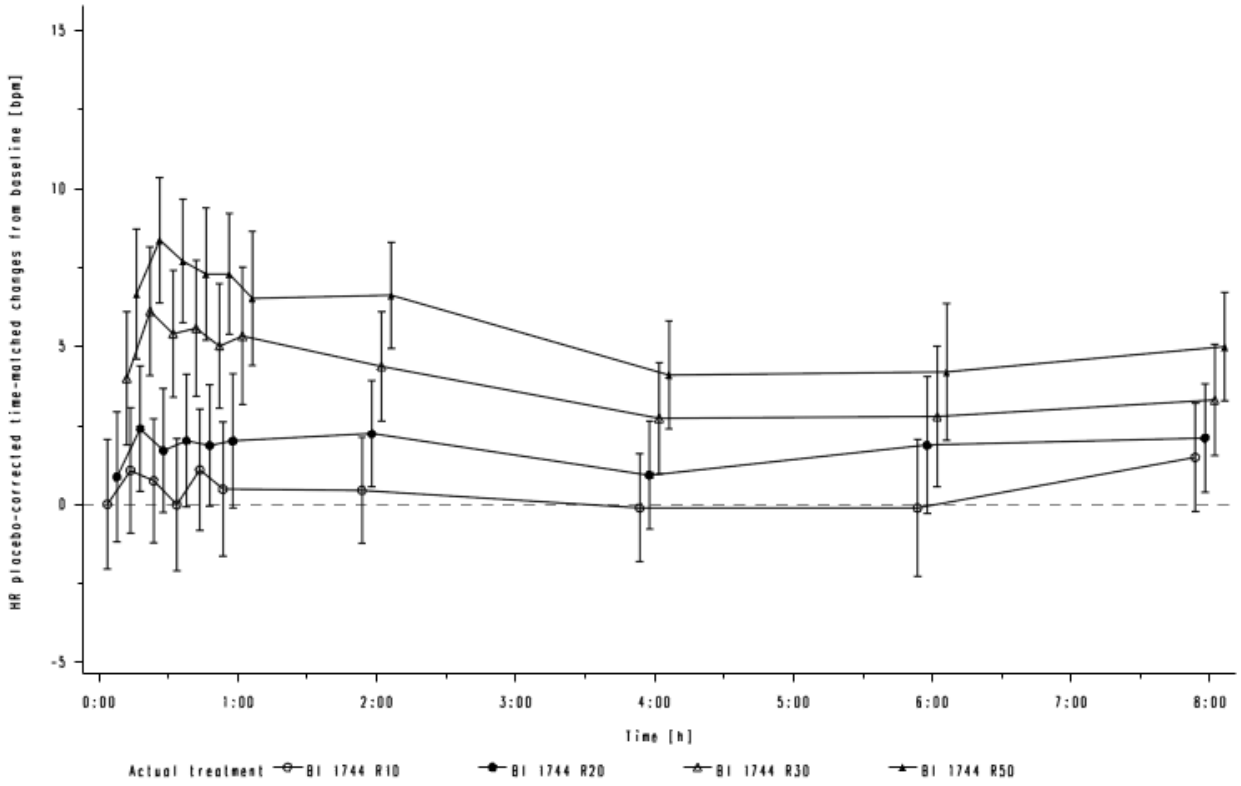
Olodaterol:
The effect of olodaterol on ECG parameters was investigated in 24 healthy volunteers in a double-blind, randomised, placebo- and active (moxifloxacin) controlled, 6-way crossover study. Olodaterol was studied at single supratherapeutic doses of 10, 20, 30 and 50 mcg.
At the 10 mcg dose, no statistically significant effects on the QTc interval, QRS duration, PR interval, or heart rate were observed.

At the 20 to 50 mcg doses, increases in the *QTcN interval were observed that were maximal at 40 min post-dosing. At the 40 min time point, the placebo-adjusted mean time-matched changes from baseline in QTcN [ms] were 0.9 (90% CI -2.3, 4.1) at the 10 mcg dose, 6.1 (90% CI 2.9, 9.3) at the 20 mcg dose, 7.4 (90% CI 4.1, 10.7) at the 30 mcg dose, and 7.9 (90% CI 4.7, 11.1) at the 50 mcg dose.



*QTcN=QT/$RR^{0.21}$ (population heart rate-corrected QT interval)

At the 20 to 50 mcg doses, dose-dependent increases in heart rate were observed that were maximal at 20 min post-dosing. At the 20 min time point, the placebo-adjusted mean time-matched changes from baseline in heart rate [bpm] were 1.1 (90% CI -0.9, 3.1) at 10 mcg, 2.4 (90% CI 0.4, 4.4) at 20 mcg, 6.1 (90% CI 4.1, 8.2) at 30 mcg, and 8.4 (6.4, 10.4) at 50 mcg.



C_{max} values for the 10 mcg, 20 mcg, 30 mcg, and 50 mcg single doses in this study were 3.3 pg/mL, 5.3 pg/mL, 9.6 pg/mL, and 16.2 pg/mL, respectively. The C_{max} for the 5 mcg therapeutic dose at steady-state in patients with COPD is expected to average 4 pg/mL.

The effect of 5 mcg and 10 mcg olodaterol 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 mcg, 10 mcg and placebo.

Tachyphylaxis

In the 48-week trials, the bronchodilator effects of olodaterol were maintained throughout the treatment period.

INSPIOLTO RESPIMAT

In two 52-week randomized, double-blind trials using INSPIOLTO RESPIMAT that enrolled 5162 patients with COPD, ECG assessments were performed post-dose on days 1, 85, 169, and 365. In a pooled analysis the number of subjects with changes from baseline-corrected QT interval of >30 msec using both the Bazett (QTcB) and Fredericia (QTcF), corrections of QT for heart rate ranged from 4.9-6.4% (QTcB) and 1.3-4.7% (QTcF) for the INSPIOLTO RESPIMAT group compared to

5.0-6.0% (QTcB) and 1.3-4.4% (QTcF) for olodaterol 5 mcg and 5.3-6.6% (QTcB) and 2.1-4.6% (QTcF) for tiotropium 5 mcg across the assessments conducted.

Pharmacokinetics

Table 3: Summary of Olodaterol and Tiotropium Pharmacokinetic Parameters

C_{max} (pg/mL)	$t_{½}$ (h)	AUC (pg·h/mL)	Clearance (mL/min)	Volume of distribution (L)
Tiotropium				
13.9 (64.7) [1]	27-45[2]	69.4 (33.2)[3]	880 (22.1)[4]	2665 (27.8) [4]
Olodaterol				
4.39 (49.2)[1]	45.1 (36.0) [5]	33.2 (66.1)[3]	872 (33.5) [6]	1110 (29.5) [6]

[1] Geometric mean (gCV%) maximum plasma concentration from COPD patients treated once daily for 4 weeks with INSPIOLTO RESPIMAT (5/5 mcg)
[2] Geometric mean effective half-life from COPD patients following once daily treatment with 18 mcg Tiotropium HandiHaler® for 14 days
[3] Geometric mean (gCV%) AUC over the 24-hour dosing interval from COPD patients following once daily treatment with INSPIOLTO RESPIMAT (5/5 mcg) for 6 weeks
[4] Geometric mean (gCV%) values from healthy volunteers administered single dose of 14.4 mcg tiotropium via intravenous infusion
[5] Geometric mean (gCV%) terminal half-life determined in healthy volunteers following 2 weeks inhalation of 30 mcg olodaterol
[6] Geometric mean (gCV%) values determined following intravenous administration of olodaterol to healthy volunteers

When tiotropium and olodaterol were administered in combination by the inhaled route, the pharmacokinetic parameters for each component were similar to those observed when each active substance was administered separately.

Absorption:

Tiotropium:

Following inhalation by young healthy volunteers, urinary excretion data suggests that approximately 33% of the dose reaches the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Food is not expected to influence the absorption of tiotropium. Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation. At steady state, peak tiotropium plasma concentrations of 10.5 pg/mL were achieved in COPD patients and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.60 pg/mL and was reached by day 7 with no accumulation thereafter.

Olodaterol:
Olodaterol is rapidly absorbed, reaching maximum plasma concentrations generally within 10 to 20 minutes following drug inhalation. Olodaterol showed linear pharmacokinetics with a dose-proportional increase of systemic exposure after single inhaled doses of 5 to 70 mcg and multiple once daily inhaled doses of 5 to 20 mcg.

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

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. Across-study comparisons however suggest somewhat higher systemic exposure in COPD patients than in healthy subjects (~34% higher steady state C_{max}, ~23% higher steady state AUC_{0-1}). Maximum olodaterol plasma concentrations generally are reached within 10 to 20 minutes following drug inhalation via RESPIMAT.

Distribution:
Tiotropium:
The drug has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier to any relevant extent.

Olodaterol:
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%.

Metabolism:
Tiotropium:
The extent of biotransformation is small. This is evident from a urinary excretion of approximately 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, both not binding to muscarinic receptors.

In-vitro experiments with human liver microsomes and human hepatocytes suggest that some further drug (<20% of dose after intravenous administration) is metabolized by cytochrome P450 dependent oxidation and subsequent glutathione conjugation to a variety of Phase II-metabolites. This enzymatic pathway can be inhibited by the CYP450 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a smaller part of the dose. Tiotropium bromide even in supra-therapeutic concentrations does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Olodaterol:
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.

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.

Excretion:
Tiotropium:
The effective half-life of tiotropium bromide ranges between 27 to 45 h following inhalation by COPD patients.

Intravenously administered tiotropium bromide to young healthy volunteers is mainly excreted unchanged in urine (74%) with a total clearance of 880 mL/min.

Following 21-day, once daily inhalation of the solution by patients with COPD, 24-hour urinary excretion is 18.6% (0.93 mcg) of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the feces.

The renal clearance of tiotropium exceeds the creatinine clearance indicating secretion into the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Olodaterol:
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 hrs. The terminal half-life following inhalation in contrast is about 45 hrs, indicating that the latter is determined by absorption rather than by elimination processes.

Following intravenous administration of [^{14}C]-labelled olodaterol, 42.5% 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.

Clinical Pharmacology

24-hour Bronchodilatory Profile:

The 24-hour lung function profiles of INSPIOLTO RESPIMAT compared to placebo was assessed in patients with moderate to severe COPD (n=219) in a six-week randomized, double-blind, placebo-controlled, cross-over trial. The primary efficacy endpoint was the forced expiratory volume in 1 second (FEV_1) AUC_{0-24} hour response (L) after 6-weeks of treatment.

After 6 weeks of treatment, INSPIOLTO RESPIMAT showed a significantly greater FEV_1 response compared to tiotropium 5 mcg, olodaterol 5 mcg and placebo over the full 24 hour dosing interval (Figure 1, Table 4).

Figure 1: FEV_1 profile for INSPIOLTO RESPIMAT, tiotropium 5 mcg, olodaterol 5 mcg and placebo over a continuous 24 hour dosing interval after 6 weeks (Trial 1237.20)

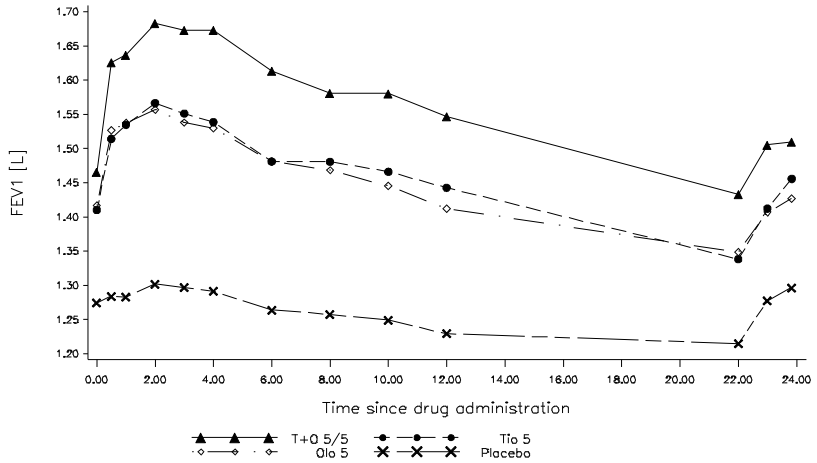


Table 4: Difference in FEV_1 (L) for INSPIOLTO RESPIMAT compared to tiotropium 5 mcg, olodaterol 5 mcg and placebo over a continuous 24 hour dosing interval after 6 weeks (Trial 1237.20)

	n	3 hr average	n	12 hr average	24 hr average[1]	Trough
INSPIOLTO RESPIMAT versus	138		138			
Tiotropium 5 mcg	137	0.109	135	0.119	0.110	0.079
Olodaterol 5 mcg	138	0.109	136	0.126	0.115	0.092
Placebo	135	0.325	132	0.319	0.280	0.207

pre-treatment baseline FEV1 = 1.30 L
[1] primary endpoint
p<0.0001 for all comparisons

More information on lung function from the pivotal studies is found in the CLINICAL TRIALS section under **Study results -** *Lung Function*.

Special Populations and Conditions

Pediatrics: The safety and effectiveness of INSPIOLTO RESPIMAT in the pediatric population have not been established.

Geriatrics: Elderly patients can use INSPIOLTO RESPIMAT at the recommended dose.
Tiotropium: As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance from 347 mL/min in COPD patients <65 years to 275 mL/min in COPD patients ≥65 years. This did not result in a corresponding increase in $AUC_{0-6,ss}$ or $C_{max,ss}$ values.

Gender: Subgroup analyses based on gender did not reveal any interactions that require special consideration.

Race: Comparison of pharmacokinetic data within and across studies with olodaterol revealed a trend for higher systemic exposure in Japanese (approximately 1.7-fold) and other Asians (1.2-fold) than in Caucasians.

Hepatic Insufficiency:
Tiotropium: The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. However, impaired liver function is not expected to have any clinically relevant influence on tiotropium pharmacokinetics since tiotropium is predominantly cleared by renal elimination and by non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.

Olodaterol: 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.

Renal Insufficiency:
Tiotropium: Once daily inhaled administration of tiotropium to steady-state in COPD patients with mild renal impairment (creatinine clearance 60-90 mL/min) resulted in slightly higher $AUC_{0-6,ss}$ (between 6% to 23% higher) and $C_{max,ss}$ (between 6% to 17% higher) values compared to patients with normal renal function. Moderate renal impairment (creatinine clearance 30-60 mL/min) resulted in modestly higher $AUC_{0-6,ss}$ (between 54% to 57% higher) and $C_{max,ss}$ (between 15% to 31% higher) values compared to COPD patients with normal renal function (creatinine clearance >90 mL/min). In patients with severe renal impairment (creatinine clearance <30 mL/min), a single intravenous administration of tiotropium bromide resulted in approximately 94% higher AUC_{0-4} and 52% higher C_{max} compared to patients with normal renal function.

Olodaterol: In subjects with severe renal impairment (CL_{CR} <30 mL/min) systemic exposure to olodaterol was on average 1.4-fold increased, up to a maximum 2-fold higher compared to healthy volunteers. As well, renal clearance and urinary excretion was lower in renal impaired patients compared to their healthy counterparts. No dose adjustment is required in these patients.

STORAGE AND STABILITY

Store at 15°C–30°C. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

Prior to first use, the INSPIOLTO RESPIMAT cartridge is inserted into the INSPIOLTO RESPIMAT inhaler and the unit is primed.

When using the unit for the first time, patients are to actuate the inhaler toward the ground until an aerosol (soft mist) cloud is visible and then repeat the process three more times. The unit is then considered primed and ready for use. If used every day, no further priming is necessary. If not used for more than 7 days, patients are to actuate the inhaler once to prepare the inhaler for use. If not used for more than 21 days, patients are to actuate the inhaler until an aerosol (soft mist) cloud is visible and then repeat the process three more times to prepare the inhaler for use (see-PART III: CONSUMER INFORMATION – PROPER USE OF THIS MEDICATION).

When the labeled number of metered actuations (60 or 28) has been dispensed from the inhaler, the INSPIOLTO RESPIMAT locking mechanism will be engaged and no more actuations can be dispensed.

After insertion of the cartridge into the inhaler, INSPIOLTO RESPIMAT should be discarded at the latest 3 months after first use or when the locking mechanism is engaged (60 or 28 actuations), whichever comes first.

Keep out of reach of children. Do not spray into eyes.

DOSAGE FORMS, COMPOSITION AND PACKAGING

INSPIOLTO RESPIMAT is supplied in a carton containing one INSPIOLTO RESPIMAT cartridge and one INSPIOLTO RESPIMAT inhaler.

The INSPIOLTO RESPIMAT cartridge is an aluminum cylinder with a tamper protection seal on the cap. The drug product, INSPIOLTO RESPIMAT, is composed of an aqueous solution of tiotropium and olodaterol filled into a plastic container crimped into an aluminum cylinder (INSPIOLTO RESPIMAT cartridge) for use with the INSPIOLTO RESPIMAT inhaler.

The INSPIOLTO RESPIMAT inhaler is a propellant free hand-held, pocket-sized, multi-dose, oral inhalation device. The INSPIOLTO RESPIMAT inhaler is a cylindrical-shaped plastic inhalation device with a grey-colored body and a clear base. The clear base is removed to insert the cartridge. The inhaler contains a dose indicator and a locking mechanism that engages after the declared number of doses has been delivered. The light green colored cap on the INSPIOLTO RESPIMAT inhaler is color coded to match the INSPIOLTO RESPIMAT cartridge and the information on the

cartridge label indicates that it should be used with the INSPIOLTO RESPIMAT inhaler.

The INSPIOLTO RESPIMAT cartridge when used with the INSPIOLTO RESPIMAT inhaler, is designed to deliver 60 or 28 metered actuations after preparation for use; the equivalent of 30 or 14 days medication when used according to the directions for use (one dose equals two actuations).

Each dose (1 dose equals 2 actuations) from the INSPIOLTO RESPIMAT inhaler delivers 5 mcg tiotropium and 5 mcg olodaterol from the mouthpiece.

As with all inhaled drugs, the actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the inhaler and inspiration through the delivery system. The duration of inspiration should be at least as long as the spray duration (1.5 seconds).

Excipients include purified water, benzalkonium chloride, disodium edetate, and hydrochloric acid.

The INSPIOLTO RESPIMAT cartridge is only intended for use with the INSPIOLTO RESPIMAT inhaler.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

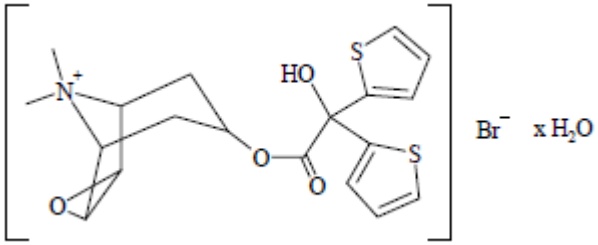
Drug Substance

Proper name: tiotropium bromide monohydrate

Chemical name: (1α,2β,4β,5α,7β)-7-[Hydroxydi-2-thienylacetyl)oxy]-9,9dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide monohydrate

Molecular formula and molecular mass: $C_{19}H_{22}NO_4S_2Br \bullet H_2O$ / 490.4 (monohydrate)
$C_{19}H_{22}NO_4S_2Br$ / 472.4 (anhydrous)

Structural formula:



Physicochemical properties:

Description:	White or yellowish white powder. It is sparingly soluble in water and soluble in methanol.
Polymorphism:	Three crystalline forms are possible, the monohydrate and two anhydrous forms
Melting Point:	Between 225ºC and 235ºC
pH (1% aqueous solution):	5.0 - 5.6
Apparent Partition Coefficient:	log P_{app} = -2.28

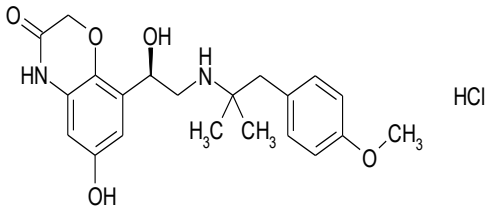
Drug Substance

Proper name: olodaterol hydochloride

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

Molecular formula and molecular mass: $C_{21}H_{26}N_2O_5$ x HCl / 422.91g/mol (hydrochloride)
$C_{21}H_{27}N_2O_5Cl$ / 386.45g/mol (free base)

Structural formula:



Physicochemical properties:

Description:	White to off-white powder
Melting Point:	210 – 220°C (DSC)
pH dependent solubility:	Sparingly - slightly soluble (> 20 -1.1 mg/ml) over the entire pH-range. The solubility in water is more than 20 mg/ml at intrinsic pH of 6.2.
Solubility in organic solvents:	• methanol freely soluble (250 mg/ml) • ethanol soluble (40 mg/ml) • 2-propanol slightly soluble (2 mg/ml) • acetone sparingly soluble (20 mg/ml)
Polymorphism:	Polymorphs have not been observed.

CLINICAL TRIALS

Pivotal Clinical Trials

Trial Design and Patient Demographics

The long-term efficacy and safety of INSPIOLTO RESPIMAT was evaluated in two replicate, 52 week randomized, double-blind, parallel group trials (i.e. trials 1237.5 and 1237.6) comparing INSPIOLTO RESPIMAT with tiotropium 5 mcg and olodaterol 5 mcg (1029 received INSPIOLTO RESPIMAT).

These trials have identical study design including study objectives, efficacy and safety endpoints, inclusion/exclusion criteria, concomitant/restricted medications, and statistical analysis methods. In these trials, the comparator products, tiotropium 5 mcg, olodaterol 5 mcg were administered via the RESPIMAT® inhaler (Table 5).

The primary efficacy endpoints were change from pre-treatment baseline (response) in forced expiratory volume in one second area under the curve (FEV_1 AUC_{0-3h}, up to 3 hours post-dose) and trough FEV_1 (23-24 hours post dose) after 24 weeks. Other efficacy endpoints that were captured after 24 weeks of treatment included the St. George's Respiratory Questionnaire (SGRQ) to measure the health-related quality of life and the Mahler Transition Dyspnea Index (TDI) as a measure of dyspnea.

Table 5: Summary of trial design and patient demographics for pivotal clinical trials

Study #	**Trial design**	**Dosage** (oral inhalation)	**Study subjects (N)** **Mean age (Range)** **Gender (%)**	**Primary Efficacy Endpoints**
1237.5	52-week treatment, randomized, double-blind, active-controlled, parallel group	Tio+Olo 2.5/5 mcg Tio+Olo 5/5 mcg Tio 2.5 mcg Tio 5 mcg Olo 5 mcg	N = 2624 64.2 yrs (40-89) M: 73.7% F: 26.3%	FEV_1 AUC_{0-3} and Trough FEV_1 at 24 weeks
1237.6	52-week treatment, randomized, double-blind, active-controlled, parallel group	Tio+Olo 2.5/5 mcg Tio+Olo 5/5 mcg Tio 2.5 mcg Tio 5 mcg Olo 5 mcg	N = 2538 63.8 yrs (40-97) M: 72.0% F: 28.0%	FEV_1 AUC_{0-3} and Trough FEV_1 at 24 weeks

A total of 5,162 subjects were randomized and treated in 52 week pivotal studies. The subjects had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a relatively stable airway obstruction with a post-salbutamol FEV_1 <80% of predicted normal values and a post-bronchodilator $FEV_1/FVC < 0.7$). Concurrent use of long-acting

bronchodilators and combinations of inhaled corticosteroids (ICS) and bronchodilators was not allowed. Concurrent use of ICS and oral corticosteroid at a stable dose, and study-provided rescue short acting beta agonist (SABA) was allowed. Subjects with a current diagnosis of asthma, clinically significant uncontrolled disease, a clinically significant laboratory finding, or a diagnosis of paroxysmal tachycardia, unstable cardiac arrhythmia, active tuberculosis, or a history of myocardial infarction or heart failure within the past year were excluded from these trials.

The majority of the 5,162 patients randomized and treated in the 52 week pivotal trials were male (73%), white (71%) or Asian (25%), with a mean age of 64.0 years. Mean post-bronchodilator FEV_1 was 1.37 L (GOLD II [50%], GOLD III [39%], and GOLD IV [11%]). Mean β_2-agonist responsiveness was 16.6% of baseline (0.171 L). Pulmonary medications allowed as concomitant therapy included inhaled steroids [47%] and xanthine´s [10%].

Study results

Lung Function

In the 52 week pivotal trials, significant improvements were observed in FEV_1 $AUC_{0\text{-}3h}$ response and trough FEV_1 response after 24 weeks (lung function primary endpoints) for INSPIOLTO RESPIMAT compared to tiotropium 5 mcg and olodaterol 5 mcg (Table 6).

Table 6: Difference in FEV_1 $AUC_{0\text{-}3h}$ and trough FEV_1 response for INSPIOLTO RESPIMAT compared to tiotropium 5 mcg, olodaterol 5 mcg after 24 weeks (Trials 1237.5 and 1237.6)

	FEV_1 $AUC_{0\text{-}3h}$ response				Trough FEV_1 response			
	Trial 1237.5		Trial 1237.6		Trial 1237.5		Trial 1237.6	
	Mean (L)	95%CI (L)	Mean	95%CI	Mean	95%CI	Mean	95%CI
INSPIOLTO RESPIMAT versus Tiotropium 5 mcg	0.117	0.094, 0.140	0.103	0.078, 0.127	0.071	0.047, 0.094	0.050	0.024, 0.075
INSPIOLTO RESPIMAT versus Olodaterol 5 mcg	0.123	0.100, 0.146	0.132	0.108, 0.157	0.082	0.095, 0.106	0.088	0.063, 0.113

pre-treatment baseline FEV_1: Trial 1237.5 = 1.16 L; Trial 1237.6 = 1.15 L
$p \leq 0.0001$ for all comparisons

INSPIOLTO RESPIMAT, administered once daily in the morning, provided clear improvement in lung function within 5 minutes after the first dose compared to tiotropium 5 mcg (mean increase in FEV_1 of 0.137 L for INSPIOLTO RESPIMAT vs. 0.058 L for tiotropium 5 mcg [$p<0.0001$] and 0.125 L for olodaterol 5 mcg [$p=0.16$]).

The increased bronchodilator effects of INSPIOLTO RESPIMAT compared to tiotropium 5 mcg and olodaterol 5 mcg were maintained throughout the 52 week treatment period (Figures 2 and 3).

Figure 2: Adjusted mean trough FEV_1 (L) response over 52 weeks of treatment, trial 1237.5

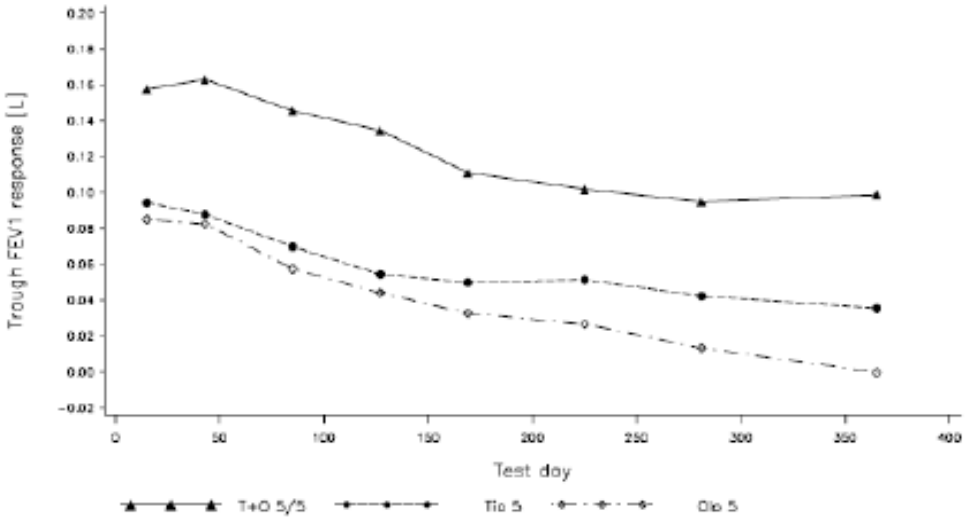
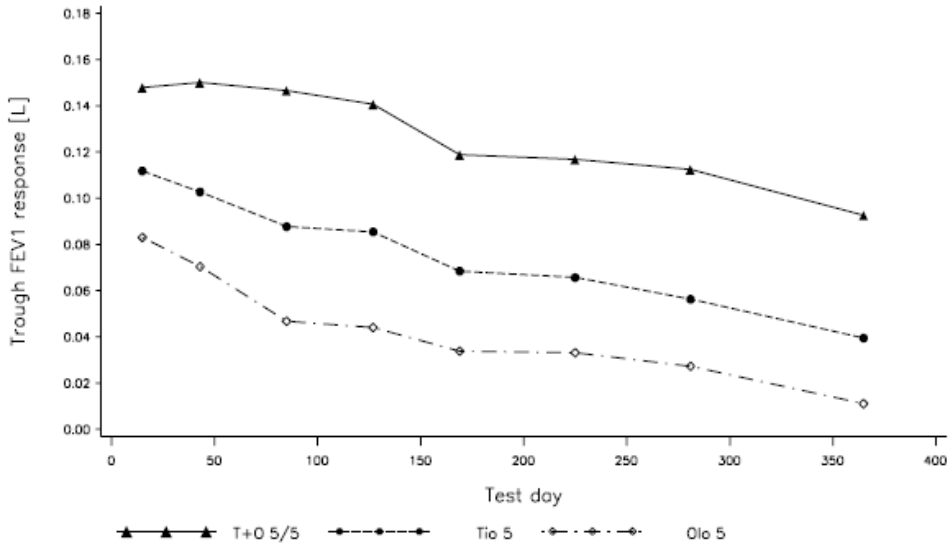
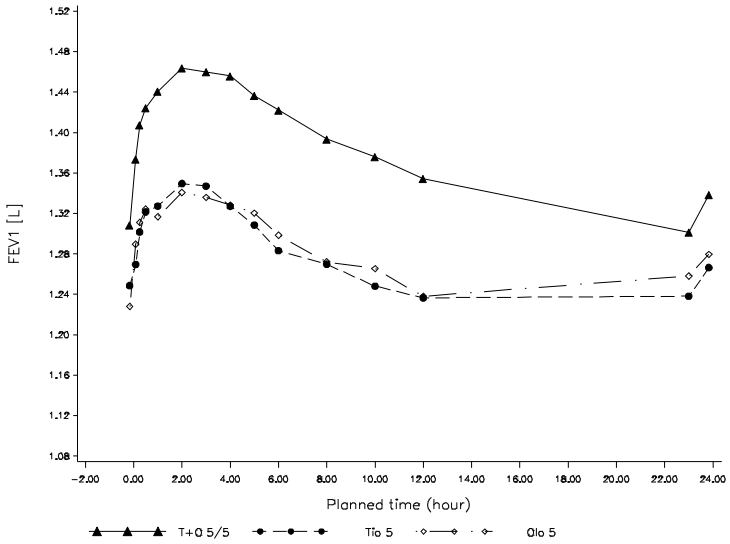


Figure 3: Adjusted mean trough FEV_1 (L) response over 52 weeks of treatment, trial 1237.6



In the sub-set of patients who completed extended lung function measurements up to 12 hrs post-dose, INSPIOLTO RESPIMAT showed a significantly greater FEV_1 response compared to tiotropium 5 mcg and olodaterol 5 mcg over the full 24 hour dosing interval (Figure 4). More information on the 24 hour bronchodilatory profile is found in **Clinical Pharmacology - 24-hour Bronchodilatory Profile:**

Figure 4: **FEV_1 profile for INSPIOLTO RESPIMAT, tiotropium 5 mcg and olodaterol 5 mcg over a continuous 24 hour dosing interval after 24 weeks (12 hr PFT sub-set from Trials 1237.5 and 1237.6; combined dataset)**



Symptom Related Outcomes

Health-related Quality of Life

Health-related quality of life was measured using St. George's Respiratory Questionnaire (SGRQ) in the pivotal trials. After 24 weeks, INSPIOLTO RESPIMAT improved mean SGRQ total score compared to tiotropium 5 mcg (-1.23 units, 95%CI -2.31, -0.15) and olodaterol 5 mcg (-1.69 units, 95%CI -2.78, -0.61); improvements were seen in all SGRQ domains. More patients treated with INSPIOLTO RESPIMAT had a clinically meaningful improvement in SGRQ total score (MCID, defined as a decrease of at least 4 units from baseline) compared to tiotropium 5 mcg (57.5% vs. 48.7%) and olodaterol 5 mcg (57.5% vs. 44.8%).

Dyspnea

After 24 weeks, INSPIOLTO RESPIMAT demonstrated an improvement in reducing shortness of breath, as measured by mean TDI focal score when compared to tiotropium 5 mcg (0.36 units; 95%CI= 0.09 to 0.62) and olodaterol 5 mcg (0.42 units, 95%CI= 0.16 to 0.68). More patients treated with INSPIOLTO RESPIMAT had a clinically meaningful improvement in TDI focal score (MCID, defined as a value of at least 1 unit) compared to tiotropium 5 mcg (54.9% vs. 50.6%) and olodaterol 5 mcg (54.9% vs. 48.2%).

Rescue Medication Use

Patients treated with INSPIOLTO RESPIMAT used less daytime and night-time rescue salbutamol compared to patients treated with tiotropium 5 mcg and olodaterol 5 mcg.

Supporting Clinical Trials (Exercise Endurance)

Trial Design

The effect of INSPIOLTO RESPIMAT on inspiratory capacity, breathing discomfort and symptom-limited exercise endurance was investigated in two replicate, 6 week randomized, double-blind, placebo-controlled, cross-over trials comparing INSPIOLTO RESPIMAT with tiotropium 5 mcg, olodaterol 5 mcg and placebo during constant work rate cycling (450 received INSPIOLTO RESPIMAT) [Trials 1237.13 and 1237.14], and one 12 week randomized, double-blind, placebo-controlled, parallel group trial comparing INSPIOLTO RESPIMAT with placebo during constant work rate cycling (139 received INSPIOLTO RESPIMAT) and constant speed walking (sub-set of patients) [Trial 1237.15].

The primary efficacy endpoints in trials 1237.13 and 1237.14 were inspiratory capacity (IC) at rest and endurance time (ET) during constant work rate cycle ergometry (CWRCE) to symptom limitation at 75% maximal work capacity (Wcap) after 6 weeks of treatment. The primary efficacy endpoints in trial 1237.15 was endurance time (ET) during constant work rate cycle ergometry (CWRCE) to symptom limitation at 75% maximal work capacity (Wcap) after 12 weeks of treatment while inspiratory capacity (IC) at rest was evaluated as a secondary endpoint.

Study Results

INSPIOLTO RESPIMAT significantly improved inspiratory capacity (IC) compared to tiotropium 5 mcg, olodaterol 5 mcg and placebo after 6 weeks (Trials 1237.13 and 1237.14; Table 7) and compared to placebo after 12 weeks (0.234 L, p<0.0001; Trial 1237.15).

Table 7: Difference in inspiratory capacity at rest (IC) (L) and 95%CI for INSPIOLTO RESPIMAT compared to tiotropium 5 mcg, olodaterol 5 mcg and placebo after 6 weeks (Trials 1237.13 and 1237.14)

	n	Trial 1237.13 [1]	n	Trial 1237.14[2]
INSPIOLTO RESPIMAT versus	219		218	
Tiotropium 5 mcg	213	0.114 (0.061, 0.167)	208	0.088 (0.039, 0.137)
Olodaterol 5 mcg	214	0.119 (0.065, 0.172)	208	0.080 (0.031, 0.129)
Placebo	211	0.244 (0.191, 0.298)	202	0.265 (0.215, 0.315)

[1] pre-treatment baseline: 2.53 L, all p values <0.0001
[2] pre-treatment baseline: 2.59 L, all p values < 0.0015

In Trials 1237.13 and 1237.14, INSPIOLTO RESPIMAT improved endurance time during constant work rate cycling by 20.9% (p<0.0001) and 13.4% (p<0.0001) respectively, when compared to placebo after 6 weeks of treatment. In Trial 1237.15, INSPIOLTO RESPIMAT improved endurance time during constant work rate cycling by 13.8% (p=0.0209) after 12 weeks compared to placebo.

Supporting Clinical Trials (Symptom Related Outcomes)

In two 12-week, placebo-controlled clinical trials, SGRQ total score at 12 weeks was also evaluated as a measure of health-related quality of life. INSPIOLTO RESPIMAT demonstrated an improvement compared with placebo at week 12 in mean SGRQ total score (primary endpoint) of -4.9 (95%CI: −6.9, −2.9) and -4.6 (95%CI: −6.5, −2.6). In a pooled analysis of the 12-week trials, INSPIOLTO RESPIMAT demonstrated an improvement compared with tiotropium 5 mcg at week 12 in mean SGRQ total score of −2.1 (95%CI: −3.5,−0.7). In the pooled analysis, the proportion of patients with a clinically meaningful decrease in SGRQ total score (defined as a decrease of at least 4 units from baseline) at week 12 was greater for INSPIOLTO RESPIMAT (52%) compared with tiotropium 5 mcg (41%) and placebo (32%).

Supporting Clinical Trials (Exacerbations)

Tiotropium 5mcg has previously demonstrated a statistically significant reduction in risk of a COPD exacerbation compared to placebo.

In a one-year, randomized, double-blind, active-controlled parallel group clinical trial, INSPIOLTO RESPIMAT was compared with tiotropium 5 mcg on COPD exacerbations. Exacerbations were defined as "a complex of lower respiratory events/symptoms (increase or new onset) related to the underlying COPD, with duration of three days or more, requiring a prescription of antibiotics and/or systemic steroids and/or hospitalization." Enrolled patients (3939 patients receiving INSPIOLTO RESPIMAT and 3941 patients receiving tiotropium 5 mcg) had a history of COPD exacerbation in the previous 12 months. All respiratory medications except anticholinergics, long-acting beta-agonists and combinations thereof were allowed as concomitant treatment, i.e. rapidly acting beta-agonists, inhaled corticosteroids and xanthines. The primary efficacy endpoint was the annualized rate of moderate to severe COPD exacerbations. The majority of patients were male (71%) and Caucasian (79%). The mean age was 66 years, and mean post-bronchodilator FEV1 percent predicted was 45%. INSPIOLTO RESPIMAT treatment did not demonstrate superiority to tiotropium 5 mcg for the primary endpoint, the annualized rate of moderate to severe COPD exacerbations, with a rate ratio of 0.93 (99% CI, 0.85-1.02, p=0.0498). The study did not reach the pre-specified significance level of $p<0.01$.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacological effects seen with tiotropium or olodaterol in nonclinical studies were those typically associated with either muscarinic antagonist or beta$_2$-agonists.

Human Pharmacology

Please refer to ACTION AND CLINICAL PHARMACOLOGY

TOXICOLOGY

Toxicological effects seen with tiotropium or olodaterol in nonclinical studies were those typically associated with either muscarinic antagonist or beta$_2$-agonists and/or local irritancy.

Tiotropium:

Acute Toxicity

The acute inhalation and oral toxicity in mice, rats and dogs was low and independent of the formulation type used (aqueous aerosol, lactose powder). Non-lethal dosages produced clinical signs characteristic of the pharmacodynamic activity of tiotropium (mydriasis, dry mouth and nose) as well as non-specific signs of toxicity (dyspnea, tremor, ataxia, convulsions, loss of motility and body weight). In mice, deaths occurred at 131 mg/kg tiotropium when administered as an aqueous aerosol through nose only exposure (the LD_{50}-value could not be established). No lethal dosage was achieved by the inhalation of either formulation in rats (LD_{50} > 334.5 mg/kg) or dogs (LD_{50} > 3.6 and > 0.7 mg/kg). Necropsy of decedents revealed pulmonary emphysema and/or congestion of liver and kidneys. No gross lesions were detected among survivors. The oral LD_{50} for mice and rats are 219,099 and 1,279,279 times respectively the maximum recommended human dose on a mg/m^2 basis.

Chronic Toxicity

The repeated-dose toxicity was investigated by inhalation of tiotropium by rats and Beagle dogs for 13 and 52 weeks, by intravenous injection over 4 weeks, and by oral gavage for 13 weeks. In rats and dogs, most in-life and morphological changes were directly or indirectly attributable to the anticholinergic activity of the compound. These changes included mydriasis, increased heart rate, and dry mucous membranes due to lowered secretory activity of the lacrimal glands as well as of the glands of the digestive and upper respiratory tract. The anticholinergic activity of the compound most probably also accounted for distension of the large bowel, and for the species-specific deposition of proteinaceous material in the urinary bladder of male rats. Subsequently, secondary indirect changes developed, such as rhinitis and keratoconjunctivitis sicca, as well as decreased food consumption, body weight gain, liver lipids, serum glucose and triglycerides. Thymic involution and changes of the Harderian gland including chromodacryorrhea were regarded as non-specific responses to stress.

Even low dosages induced signs characteristic of the anticholinergic activity of tiotropium; therefore, a no observed toxic event level (NOTEL) could only be established in a limited number of studies. In the rat, the inhalation NOTEL was < 0.013 mg/kg and the inhalation NOTEL in the dog was > 0.010 mg/kg. The few changes that were perhaps unexpected include urogenital tract changes and cataracts in rats. The urogenital changes are nevertheless considered as sequelae to pharmacological effects and as such are part of a syndrome that includes the prostate. In view of the species-specificity of the syndrome and its harmless nature, it is unlikely to have any influence on human safety assessment. Similarly, although the precise mechanism remains unknown, cataract formation appears to be specific to Wistar rats and to the mode of administration. As the method of administration to the patient avoids direct eye exposure to tiotropium, any risk to patients is negligible.

Reproductive Toxicity

The effects of tiotropium (Ba 679 BR) administered *via* inhalation on the fertility and early embryonal development (Segment I), and on the peri- and postnatal development (Segment III) were assessed in rats, and those on the embryo-fetal development (Segment II) were investigated in rats and rabbits. Dose dependent paternal and maternal toxicity was observed. Embryo-fetal toxicity, considered secondary to maternal toxicity, was observed at high doses in rats and rabbits. There was no impairment of reproductive function of the F_0 generation and no effect on the postnatal development of the F_1 generation. The incidence of variations was increased at dose levels above 0.01 mg/kg but they were of the types encountered in the historical controls. No teratogenicity was noted.

The No Observed Toxic Effect Level (NOTEL) for maternal/paternal toxicity in the rat and rabbit was < 0.01 mg/kg Ba 679 BR and for developmental toxicity 0.01 mg/kg in all three segments when administered by inhalation.

In a general reproduction and fertility study in rats, there was no indication of any adverse effect on fertility or mating performance of either treated parents or their offspring at clinically relevant dosages.

Carcinogenicity and Mutagenicity

Inhalation carcinogenicity studies in mice and rats have revealed no carcinogenic potential at target tiotropium doses up to 2.54, 180 and 75 mcg/kg/day (male mice, female mice and rats, respectively). These doses correspond to about 0.45, 92 and 27 times the maximum recommended human dose (MRHD) on a mg/m^2 basis.

Results of various mutagenicity studies (Ames test and E coli bacterial gene mutation test, gene mutation test in V79 Chinese hamster cells, *in vitro* cytogenetic study with human lymphocytes, *in vitro* unscheduled DNA-synthesis test, and *in vivo* micronucleus test) were negative.

Olodaterol:

Acute Toxicity

Acute toxicity after single-dose inhalation, intravenous and oral administration in mice and rats, was low. Single oral administrations of olodaterol were well tolerated in mice and rats up to 1000 mg/kg and 316 mg/kg, respectively. The single-dose safety pharmacology studies showed the expected effects of a $beta_2$-adrenergic agonist including decreased blood pressure, and increased heart rate and force of contraction.

Repeat-dose Toxicity

The effects in the inhalation repeat-dose studies in mice, rats and dogs were mainly related to beta$_2$-adrenergic properties of olodaterol including increased body weight and muscle mass and food consumption (rodents). Reduced epididymides and testes weights and increased ovary and uterus weights as well as increased heart weight were commonly observed in rodents. The effects of olodaterol in the toxicity studies in dogs were mainly an increase in heart rate, changes in glycogen distribution in the liver and papillary muscle necrosis as well as an increased body weight and elevated creatine kinase and plasma creatinine levels related to the beta$_2$-adrenergic properties of olodaterol.QTc prolongation was observed in dogs only after oral administration of olodaterol. Irritancy of the upper respiratory tract in mice and rats consisting of epithelial changes of the nasal cavity and larynx and necrosis of the U shaped cartilage in the larynx were observed at all doses including vehicle and therefore may be attributed to the formulation. All these findings were observed only at exposures in excess of the human exposure at 5 mcg olodaterol. The clinical significance of these is likely of little relevance, yet they do remain unclear.

Table 8: Sub-chronic and chronic toxicology (pivotal studies, longest treatment duration only)

Study Type	Species	Route	Doses [mcg/kg/day]	Findings
13-week	CD1 Mouse	Inhalation	63, 211, 900 3258	Findings at all doses comprised excess salivation, increased body weight, food consumption, K^+values, decreased triglycerides values, increased weights of lung, spleen and heart. At ≥211 mcg/kg increased ovarian and uterus weight, squamous metaplasia of the larynx. At ≥900 mcg/kg muscle mass was mildly increased. At 3258 mcg/kg thickened uterus and myometrium and increase nos of corpora lutea and cystic glands in the endometrium. In all groups, including controls, transitional cell hyperplasia of the laryngeal epithelium. NOAEL = 63 mcg/kg/day, not considering pharmacodynamic effects
26-week	Wistar Rat	Inhalation	49, 200, 3400	Findings at all doses comprised increased body weight, food consumption, increased skeletal muscle mass and slightly elevated liver parameters, decreased white adipose tissue and degeneration of laryngeal cartilage. At 200 mcg/kg decreased liver glycogen, squamous metaplasia in the larynx and foam cells in the lungs. In addition at 3400 mcg/kg irritation of the respiratory tract, squamous metaplasia in the nasal cavities, larynx & tracheal bifurcation, hemorrhages in corpora lutea, distension of uterus horns, decreased tested weights. All findings were reversible after recovery. NOAEL = 200 mcg/kg/day, not considering pharmacodynamic effects

Study Type	Species	Route	Doses [mcg/kg/day]	Findings
52-week	Beagle Dog	Inhalation	15, 60, 330	Findings at all doses comprised increase heart force, heart rate with mitigation as the study progressed, dry mouth mucosa, increased body weight CK and plasma creatinine values, decreased prostate weight. At 60 mcg/kg ventricular arrhythmias, increased QTf, cTnI and fibrotic foci in the myocardium of left papillary muscles, change of the glycogen distribution and content in liver, glandular atrophy of the prostate were observed. In addition at 330 mcg/kg increases in blood pressure and glandular atrophy of the prostate. NOAEL = 15 mcg/kg/day, not considering pharmacodynamic effects

Reproductive Toxicity

In rats, no teratogenic effects occurred after inhalation at doses 1054 mcg/kg/day (> 2600 times the human exposure ($AUC_{(0-24h)}$) at the dose of 5 mcg). In pregnant NZW rabbits, an inhalation dose of 2489 mcg/kg/day (approximately 7130 times the human exposure at 5 mcg based on $AUC_{(0-24h)}$) 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 mcg/kg (approximately 1353 times the 5 mcg dose based on $AUC_{(0-24h)}$).

No impairment of male or female fertility or early embryonic development was seen in the rat up to inhalation doses of 3068 mcg/kg (approximately 2332 times the 5 mcg dose based on $AUC_{(0-24h)}$).

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 mcg/kg/day (approximately 2332 times the 5 mcg dose based on $AUC_{(0-24h)}$).

Table 9: Reproductive Toxicology (pivotal studies)

Study Type	Species	Route	Doses [mcg/kg/day]	Findings
Fertility, reproductive performance and early embryonic development	SD Rat	Inhalation	58, 192, 3068	Findings at all doses comprised excessive salivation, reddened skin, increased body weight, food consumption, decreased weights of testes and epididymides. At 3068 mcg/kg: subdued behavior. NOAEL paternal / maternal: = 58 mcg/kg/day, NOAEL fertility / embryonic development / mating: = 3068 mcg/kg/day

Study Type	Species	Route	Doses [mcg/kg/day]	Findings
Embryo-fetal development	SD Rat	Inhalation	64, 222, 1054	Maternal findings at all doses were increased body weight, food consumption. Embryo-fetal findings comprised increased body weight at all doses. NOAEL maternal & embryo-fetal = 1054 mcg/kg/day
Embryo-fetal development	NZW Rabbit	Inhalation	289, 974, 2489	Maternal findings at all doses were increased body weight. Embryo-fetal findings at 2489 mcg/kg comprised thickened ribs/distorted rib cage, short/bent scapula/humerus/ radius/ulna/femur/ tibia/fibula and/or limb flexure combined, partially open eye and/or cleft palate, unossified areas/patchy ossification of the cranial bones/ribs/long bones; cardiovascular abnormalities. NOAEL maternal = 2489 mcg/kg/day, NOAEL embryo-fetal = 974 mcg/kg/day
Pre- and postnatal development, including maternal function	SD Rat	Inhalation	58, 297, 3665	Maternal findings at all doses comprised increased body weight gain, salivation NOAEL F0 & F1 generation: = 3665 mcg/kg/day

Genotoxicity

In the *in vivo* rat bone marrow micronucleus assay after inhalation exposure (up to approximately 1092 times the 5 mcg dose based on $AUC_{(0-24h)}$) and the *in vitro* (Ames test, mouse lymphoma assay) mutagenicity assays, olodaterol was free of any genotoxic potential up to very high dose levels. An increased frequency of micronuclei was observed in rats after i.v. exposure at doses of at least 5500-times the 5 mcg dose based on $AUC_{(0-24h)}$ may be related to drug enhanced (compensatory) erythropoiesis.

Carcinogenicity

Lifetime treatment of rats induced class- and rodent-specific leiomyomas of the mesovarium at exposures approximately 198-fold and 18-fold the exposure at the dose of 5 mcg based on $AUC_{(0-24h)}$.. 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 42- to 318-fold the exposure at the dose of 5 mcg based on $AUC_{(0-24h)}$. Increases in leiomyomas and leiomyosarcomas of the female rodent reproductive tract have been similarly demonstrated with other β_2-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Table 10: Carcinogenicity

Study Type	Species	Route	Doses [mcg/kg/day]	Findings
Carcinogenicity	Mouse CD1	Inhalation	26, 77, 255	Findings at all doses comprised increased body weight, food consumption, muscle mass At doses ≥77 mcg/kg/day increased incidences of leiomyomas and leiomyosarcomas of the uterus, sex cord stromal focal hyperplasia and luteal focal hyperplasia of the ovary. No tumor findings were observed in male mice at doses up to 255 mcg/kg/day.
Carcinogenicity	Wistar Rat	Inhalation	26, 76, 270	Findings at all doses comprised increased body weight, food consumption, muscle mass. At doses ≥26 mcg/kg/day increased incidences of leiomyomas of the mesovarium

Tiotropium + Olodaterol

Single-dose toxicity

For the combination tiotropium + olodaterol single-dose toxicity studies after inhalation administration have been performed for three dose ratios in mice and rats, revealing a low acute toxicity. In mice, the approximate lethal doses (ALD) were 34.8+36.6 mg/kg for tiotropium + olodaterol in the ratio 1:1. In rats, no deaths occurred, therefore the ALDs were >17.9+18.8 mg/kg for tiotropium/olodaterol in the ratio 1:1.

Repeat-dose toxicity

Inhalation repeat-dose toxicity studies for the combination tiotropium + olodaterol were performed in rats (4 weeks) and dogs (up to 13 weeks) at different dose ratios. In the 13-week studies in dogs, body weight development, clinical signs, changes of the cardiovascular system and of respective enzyme activities as well as the macroscopical and microscopical pathology were characteristic β_2-agonistic and anticholinergic effects. In the 13-week toxicity studies with the dose ratio 1:1 for tiotropium/olodaterol, the no observed adverse effect levels (NOAEL) were 14+16 mcg/kg/day.

Reproduction toxicity

No reproduction toxicity studies for the combination were performed.

Genotoxicity

In vitro mutagenicity for tiotropium or olodaterol alone, did not show any genotoxic potential. In the *in vivo* rat bone marrow micronucleus assay, after inhalation at dose levels of up to 2266+2174 mcg/kg/day tiotropium + olodaterol for 4 weeks (dose ratio 1:1), the combination was free of genotoxic potential.

Carcinogenicity

No carcinogenicity studies for the combination were performed.

REFERENCES

1. Current Spiriva Respimat Product Monograph.
2. Current Striverdi Respimat Product Monograph.

PART III: CONSUMER INFORMATION

[Pr]Inspiolto® Respimat®
Tiotropium (as Tiotropium Bromide Monohydrate) / Olodaterol (as Olodaterol Hydrochloride) Inhalation Solution

Read this carefully before you start taking INSPIOLTO RESPIMAT and each time you get a refill. This leaflet is a summary and will not tell you everything about INSPIOLTO RESPIMAT. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about INSPIOLTO RESPIMAT.

ABOUT THIS MEDICATION

What the medication is used for:
INSPIOLTO RESPIMAT is a combination of two medicines that are used to make breathing easier for people who experience breathing difficulties due to a lung disease called Chronic Obstructive Pulmonary Disease or COPD (including chronic bronchitis and emphysema).

What it does:
INSPIOLTO RESPIMAT contains two active ingredients: Tiotropium, a long-acting muscarinic antagonist (LAMA), and Olodaterol, a long-acting beta$_2$-adrenergic agonist (LABA).

Tiotropium and olodaterol relax the muscles in the walls of small airways in the lungs. Both of these medicines work together to help open the airways and make it easier for air to get in and out of the lungs. When taken as prescribed, tiotropium and olodaterol help keep the airways open, which can help prevent shortness of breath and wheezing.

When it should not be used:
Do not use INSPIOLTO RESPIMAT:
- **if you have asthma;**
- **to treat sudden symptoms of COPD;**
- **if you are allergic to tiotropium bromide, ipratropium bromide or other anticholinergic drugs (containing atropine or its derivatives);**
- **if you are allergic to olodaterol hydrochloride or other drugs containing a beta agonist;**
- **if you are allergic to any of the non-medicinal ingredients in the formulation;**
- **if you are less than 18 years of age.**

What the medicinal ingredients are:
Tiotropium Bromide Monohydrate and Olodaterol Hydrochloride

What the non-medicinal ingredients are:
Benzalkonium chloride, disodium edetate, hydrochloric acid and purified water.

What dosage forms it comes in:
Inhalation solution.
Each puff delivers 2.5 mcg tiotropium (as tiotropium bromide monohydrate) and 2.5 mcg olodaterol (as olodaterol hydrochloride) from the mouthpiece.

INSPIOLTO RESPIMAT is supplied in a carton containing one INSPIOLTO RESPIMAT cartridge and one INSPIOLTO RESPIMAT inhaler.

The INSPIOLTO RESPIMAT cartridge is only intended for use with the INSPIOLTO RESPIMAT inhaler.

WARNINGS AND PRECAUTIONS

Warnings – Asthma-Related Death

You are advised that in patients with asthma, long-acting beta$_2$-agonist (LABA) medicines increase the chance of death from asthma problems. In a large asthma study, more patients who used another LABA medicine (salmeterol) died from asthma problems compared with patients who did not use that LABA medicine. This finding may also apply to INSPIOLTO RESPIMAT.
INSPIOLTO RESPIMAT should only be used to treat COPD.
INSPIOLTO RESPIMAT should not be used to treat asthma.

BEFORE you use INSPIOLTO RESPIMAT talk to your doctor, nurse or pharmacist if you:
- have heart problems, such as rapid or irregular heartbeat or abnormal electrical signal called "prolongation of the QT interval";
- have high blood pressure;
- have seizures;
- have thyroid problems;
- have diabetes;
- are taking similar medicines for your lung disease;
- have been told you react strongly to sympathomimetic amines (a class of drugs that includes LABA drugs) or if you are allergic to ipratropium bromide or other drugs which are anticholinergic (contain atropine or its derivatives);
- are taking any medications including eye drops, this includes those you can buy without a prescription;
- have any other medical problems such as difficulty with urination or enlarged prostate;
- have eye problems, such as glaucoma, or eye pain;
- have any allergies to food or drugs;
- have kidney disease;
- are pregnant or planning to become pregnant. It is not known if INSPIOLTO RESPIMAT can harm your unborn baby;
- are breastfeeding. It is not known if INSPIOLTO RESPIMAT passes into your milk and if it can harm your baby.

During the treatment with INSPIOLTO RESPIMAT, tell your doctor immediately or get emergency medical care if you experience any of the following symptoms:
- Tightness of the chest, coughing, wheezing or breathlessness immediately after inhalation (signs of bronchospasm).
- Difficulties in breathing or swallowing, swelling of tongue, lips and face, hives or itching, skin rash (signs of

hypersensitivity reaction). Do not use INSPIOLTO RESPIMAT again before speaking with your doctor.
- Your COPD symptoms (breathlessness, wheezing, cough) do not improve or if they worsen during your treatment.
- Pain or difficulty with urination.

Other warnings you should know about

Treatment of COPD: INSPIOLTO RESPIMAT does not relieve sudden symptoms of COPD. Always have a short-acting bronchodilator medicine with you to treat acute symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.

Benzalkonium chloride may cause wheezing and breathing difficulties (bronchospasm), especially if you have asthma.

Driving and using machines: Caution is required when driving a car or operating machinery as dizziness and blurred vision may occur with the use of INSPIOLTO RESPIMAT. If you experience dizziness, you should avoid driving or operating machinery.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with INSPIOLTO RESPIMAT:
- antidepressants, in particular tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs);
- medicines similar to INSPIOLTO RESPIMAT (other short- or long-acting muscarinic antagonists such as ipratropium, tiotropium, glycopyrronium, aclidinium, umeclidinium) used for your lung disease, as an overdose may result;
- medicines that decrease the level of potassium in your blood. These include diuretics (also known as "water pills" and are used to treat high blood pressure e.g. hydrochlorothiazide), other bronchodilators such as methylxanthines (e.g. theophylline) or steroids (e.g. prednisolone);
- beta-blockers used in the treatment of high blood pressure or other heart problems (e.g. propranolol) or in the treatment of glaucoma (e.g. timolol).

PROPER USE OF THIS MEDICATION

- Read the **Instructions for use** before using INSPIOLTO RESPIMAT and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor, nurse or pharmacist about your medical condition or your treatment.

- Always use the new INSPIOLTO RESPIMAT inhaler that is provided with each new prescription.

- Do not stop using INSPIOLTO RESPIMAT or other medicines to control or treat your COPD unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.

- Do not spray into eyes.

- Call your healthcare provider or get emergency medical care right away if:
  - your breathing problems worsen with INSPIOLTO RESPIMAT;
  - you need to use your rescue medicine more often than usual;
  - your rescue inhaler medicine does not work as well for you at relieving your symptoms.

Usual Adult Dose:

The recommended dose of INSPIOLTO RESPIMAT is 2 puffs (5 mcg tiotropium and 5 mcg olodaterol), once daily at the same time of the day, every day.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of INSPIOLTO RESPIMAT, take it as soon as you remember. Do not take more than one dose (two puffs) per day. Then take your next dose as usual.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:
- increase of the measured eye pressure;
- seeing halos around lights or coloured images in association with red eyes;
- blurred vision;
- diarrhea;
- constipation;
- dry mouth;
- inflammation of the mouth, gums and tongue;
- difficulty in swallowing;
- heartburn;
- feeling tired;
- general weakness;
- inflammation of the throat, nasal passages and sinuses;
- common cold;
- fungal infections of the oral cavity and throat;
- depletion of body water;
- back pain;
- swollen and painful joints;
- muscular pain;
- muscle spasms;

- feeling dizzy;
- difficulty sleeping
- cough;
- pain in mouth and throat;
- hoarseness;
- nosebleed;
- sore throat and discomfort when swallowing;
- inflammation/irritation of the vocal chords;
- pain when passing urine;
- inability to empty the bladder;
- rash;
- itching;
- nettle rash;
- infections or ulcerations of the skin;
- dryness of the skin.

If any of these affects you severely, tell your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Uncommon	**High or low blood pressure:** headache, ringing in the ears, lightheadedness, dizziness, fainting		✓	
	Fast or irregular heartbeat, heart palpitations, prolongation of QT interval		✓	
	Blockage of intestines or absence of bowel movements (intestinal obstruction, including ileus paralytic)		✓	
	Blurred vision or pain in the eyes			✓
	Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	Bronchospasm: wheezing or coughing and difficulty breathing			✓
	Urinary tract infection: pain and burning when urinating, frequent urination		✓	
Rare	**Swelling of the feet, ankles or legs (edema peripheral)**		✓	
	Bronchitis: shortness of breath, cough, chest pain		✓	
	Lower respiratory infection: shortness of breath, cough, chest pain		✓	
	Myocardial ischaemia (decreased blood flow to your heart muscle): chest pain, trouble breathing, swelling of the hands or feet, heartburn			✓
Not Known	**Chest pain**		✓	
	High blood sugar: frequent urination, thirst, and hunger	✓		
	Blood pH imbalance (metabolic acidosis): chest pain, headache, heart palpitations, nausea, vomiting, stomach pain			✓
	Low blood potassium: irregular heartbeats, muscle weakness or spasms and generally feeling unwell		✓	

This is not a complete list of side effects. For any unexpected

effects while taking INSPIOLTO RESPIMAT, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store INSPIOLTO RESPIMAT between 15–30°C. Do not freeze your INSPIOLTO RESPIMAT cartridge and inhaler. Keep your INSPIOLTO RESPIMAT cartridge and inhaler out of the sight and reach of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: *Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

MORE INFORMATION

If you want more information about INSPIOLTO RESPIMAT:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp), the manufacturer's website (https://www.boehringer-ingelheim.ca), or by calling the manufacturer, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103, ext. 84633.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd. The information in this leaflet is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

Last revised: November 14, 2019

INSTRUCTIONS FOR USE

Introduction

Read these **Instructions for Use** before you start using INSPIOLTO RESPIMAT.

You will need to use this inhaler only ONCE A DAY. Each time you use it take 2 PUFFS.

Each box contains:
- 1 RESPIMAT inhaler
- 1 cartridge

Each cartridge provides 60 puffs (30 doses). Physician samples and hospital packs provide 28 puffs (14 doses).

The colour of the cap of the RESPIMAT inhaler is colour coded to match the cartridge.

How to store my INSP

Store INSPIOLTO RES n 15-30°C. Do not freeze.

Keep out of the sight an

Do not use your inhaler after the expiry date.

Do not touch the piercing element inside the clear base.

If you have not used your inhaler in more than:
- 7 days: release 1 puff towards the ground
- 21 days: repeat steps 4 to 6 under "Prepare for First Use" until a cloud is visible**.** Then repeat steps 4 to 6 three more times.

How to care for your INSPIOLTO RESPIMAT

Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only. You should do this at least once a week. Any minor changes in the colour of the mouthpiece will not affect how your INSPIOLTO RESPIMAT works.

When to get a new INSPIOLTO RESPIMAT

- Your INSPIOLTO RESPIMAT inhaler contains either 60 puffs (30 doses) or 28 puffs (14 doses) if you use it as directed (2 puffs/once a day). The 28 puff (14 doses) product is for physician samples and the hospital pack.
- The dose indicator shows you about how much medication is left.
- When the dose indicator **enters** the red area of the scale, there is about:
  - 7 days of medication left for the 60 puff product
  - 3 days of medication left for the 28 puff product.

  You need to get a new prescription or refill your prescription.
- Once the dose indicator reaches the **end** of the red scale:
  - Your INSPIOLTO RESPIMAT locks automatically. No more doses can be released. At this point, the clear base cannot be turned any further.
- You should throw out the INSPIOLTO RESPIMAT when one of the following happens first:
  - 3 months after first use, even if all the medication has not been used, or
  - it locks automatically.

Prepare for First Use

1

Remove clear base

- Keep the cap closed.
- Press the safety catch while firmly pulling off the clear base with your other hand.

2

Insert cartridge

- Insert the **narrow** end of the cartridge into the inhaler.
- Place the inhaler on a firm surface and push down firmly until it snaps into place.
- You should hear a "**click**" when it has gone in all the way.

3

Replace clear base

- Put the clear base back into place until it **"clicks"**.
- Do not remove the clear base again.

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 to 6 **until** a cloud is visible.
- **After a cloud is visible**, repeat steps 4 to 6 three more times.

Your inhaler is now ready to use.

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 your lips around the mouthpiece without covering the air vents.
- While taking a slow, deep breath through your mouth, **PRESS** the dose-release button and continue to breathe in.
- Hold your breath for 10 seconds or for as long as you feel comfortable.

To take your second puff, repeat the 3 steps, TURN, OPEN and PRESS (TOP) one more time.
Close the cap.

Answers to Common Questions

It is difficult to insert the cartridge deep enough:	The dose indicator on the INSPIOLTO RESPIMAT reaches zero too soon:
Did you accidentally turn the clear base before inserting the cartridge? Open the cap, press the dose-release button, then insert the cartridge.	**Did you use INSPIOLTO RESPIMAT as indicated (2 puffs/once daily)?** INSPIOLTO RESPIMAT will last 30 days if used at 2 puffs once daily. Physician samples and hospital packs will last 14 days if used at 2 puffs once daily.
Did you insert the cartridge with the wide end first? Insert the cartridge with the narrow end first.	**Did you turn the clear base before you inserted the cartridge?** The dose indicator counts each turn of the clear base regardless whether a cartridge has been inserted or not. **Did you spray in the air often to check whether the INSPIOLTO RESPIMAT is working?** Once you have prepared INSPIOLTO RESPIMAT, no test-spraying is required if used daily. **Did you insert the cartridge into a used INSPIOLTO RESPIMAT?** Always insert a new cartridge into a **NEW** INSPIOLTO RESPIMAT.
I cannot press the dose-release button:	My INSPIOLTO RESPIMAT doesn't spray:
Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn). **Is the dose indicator on the INSPIOLTO RESPIMAT pointing to zero?** The INSPIOLTO RESPIMAT inhaler is locked after 60 puffs (30 doses). Physician samples and hospital packs will be locked after 28 puffs (14 doses). Prepare and use your new INSPIOLTO RESPIMAT inhaler.	**Did you insert a cartridge**? If not, insert a cartridge. **Did you repeat Turn, Open, Press (TOP) less than three times after inserting the cartridge?** Repeat Turn, Open, Press (TOP) three times after inserting the cartridge as shown in steps 4 to 6 under "Prepare for First Use". **Is the dose indicator on the INSPIOLTO RESPIMAT pointing to zero?** If the dose indicator points to zero, you have used up all your medication and the inhaler is locked. Once your INSPIOLTO RESPIMAT is assembled, do not remove the clear base or the cartridge. Always insert a new cartridge into a **NEW** INSPIOLTO RESPIMAT.
I cannot turn the clear base:	My INSPIOLTO RESPIMAT sprays automatically:
Did you turn the clear base already? If the clear base has already been turned, follow steps "OPEN" and "PRESS" under the directions for "Daily Use" to get your dose. **Is the dose indicator on the INSPIOLTO RESPIMAT pointing to zero?** The INSPIOLTO RESPIMAT inhaler is locked after 60 puffs (30 doses). Physician samples and hospital packs will be locked after 28 puffs (14 doses). Prepare and use your new INSPIOLTO RESPIMAT inhaler.	**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).