Boehringer Ingelheim's Commitment to COPD

Extensive world-wide use

SPIRIVA® HANDIHALER®:
54,476,905 patient-years[1†]

SPIRIVA® RESPIMAT®:
6,016,206 patient-years[2‡]

INSPIOLTO® RESPIMAT®:
1,702,362 patient-years[1§]

Well studied

SPIRIVA HANDIHALER:
20,517 patients[2]

SPIRIVA RESPIMAT:
15,230 patients in 36 clinical trials[2,4¶]

INSPIOLTO RESPIMAT:
9,648 patients in 23 clinical trials[5¶]

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.[3]

SPIRIVA RESPIMAT (tiotropium bromide monohydrate) is indicated as a long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and for the reduction of exacerbations.[6]

SPIRIVA (tiotropium bromide monohydrate) is indicated as a long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.[7]

† From May 2002 to August 2018. ‡ From September 2007 to September 2017. § From June 2015 to July 2019.
¶ Exposure was calculated based on number of subjects randomized/assigned and documented to have received at least 1 dose of study drug.

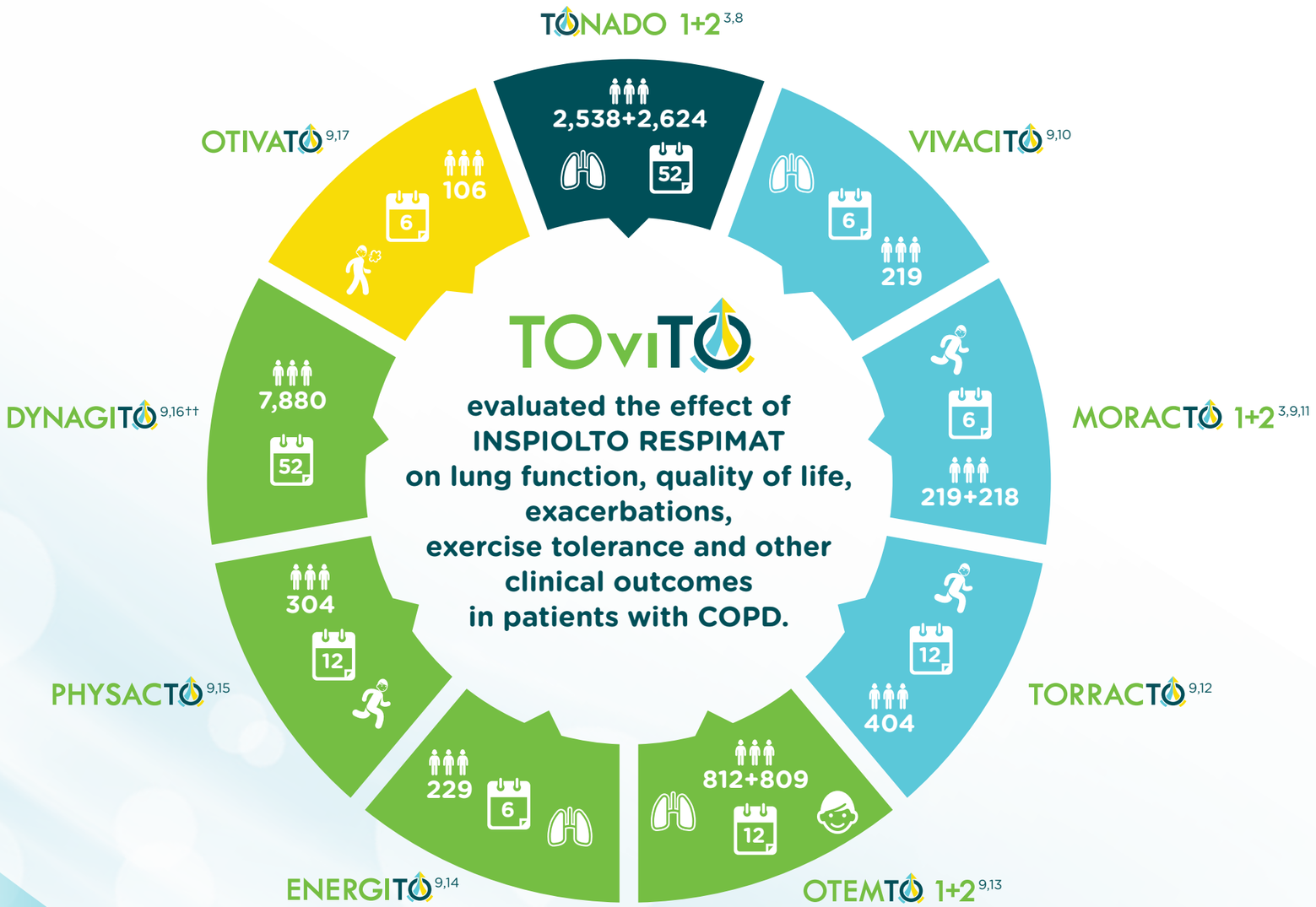
Pr INSPIOLTO® RESPIMAT®
TIOTROPIUM & OLODATEROL

Pr SPIRIVA® RESPIMAT®
(tiotropium bromide monohydrate)

Pr SPIRIVA®
(tiotropium bromide monohydrate)

With the TOviTO program

Boehringer Ingelheim studied **over 15,000 patients worldwide** in Phase III clinical trials.



- Lung function study
- Exercise endurance study
- Activity-related breathlessness
- Quality of life study
- Length of trial (weeks)
- Number of patients

Phases:

- Pivotal study
- Phase IIIa study
- Phase IIIb study
- Phase IV study

†† The DYNAGITO study did not meet the targeted 0.01 significance level (primary endpoint).

Pr INSPIOLTO® RESPIMAT®
TIOTROPIUM & OLODATEROL

TOviTO Key outcomes from the completed studies

	Primary Outcomes	Treatment Arms
TONADO 1+2[8]	At 24 weeks: • FEV_1 $AUC_{0\text{-}3h}$ • Trough FEV_1	• INSPIOLTO RESPIMAT 5/5 µg q.d. • SPIRIVA RESPIMAT 5 µg q.d. • STRIVERDI RESPIMAT 5 µg q.d.
VIVACITO[10]	• FEV_1 $AUC_{0\text{-}24h}$	• INSPIOLTO RESPIMAT 5/5 µg q.d. • SPIRIVA RESPIMAT 5 µg q.d. • STRIVERDI RESPIMAT 5 µg q.d. • Placebo
MORACTO 1+2[11]	• Inspiratory capacity at rest • Endurance time during Constant Work Rate Cycle Ergometry to symptom limitation at 75% maximal work capacity	• INSPIOLTO RESPIMAT 5/5 µg q.d. • SPIRIVA RESPIMAT 5 µg q.d. • STRIVERDI RESPIMAT 5 µg q.d. • Placebo
TORRACTO[12]	• Exercise endurance time during Constant Work Rate Cycle Ergometry to symptom limitation at 75% maximal work capacity	• INSPIOLTO RESPIMAT 5/5 µg q.d. • Placebo
OTEMTO 1+2[13]	• FEV_1 $AUC_{0\text{-}3h}$ • Trough FEV_1 • SGRQ total score	• INSPIOLTO RESPIMAT 5/5 µg q.d. • SPIRIVA RESPIMAT 5 µg q.d. • Placebo
ENERGITO[14]	• FEV_1 $AUC_{0\text{-}12h}$	• INSPIOLTO RESPIMAT 5/5 µg q.d. • Salmeterol + fluticasone 50/500 & 50/250 µg b.i.d.
PHYSACTO[15]	• Exercise endurance time measured by endurance shuttle walk test to symptom limitation after 8 weeks	• INSPIOLTO RESPIMAT 5/5 µg q.d. with BM • SPIRIVA RESPIMAT 5 µg q.d. with BM • Placebo with BM
OTIVATO[17]	• Activity-related breathlessness measured using modified Borg scale at the end of the 3-min CSST after 6 weeks	• INSPIOLTO RESPIMAT 5/5 µg q.d. • SPIRIVA RESPIMAT 5 µg q.d.

For more information, call Medical Information at 1 (800) 263-5103 Ext. 84633, or ask your Boehringer Ingelheim representative.

STRIVERDI RESPIMAT (olodaterol hydrochloride solution for inhalation) is 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 or COPD (including chronic bronchitis and emphysema).[18‡‡]

FEV_1: forced expiratory volume in one second; AUC: area under the curve; SGRQ: St. George's Respiratory Questionnaire; q.d.: once-daily; b.i.d.: twice-daily; BM: behavioural modification; CSST: constant speed shuttle test

‡‡ STRIVERDI RESPIMAT is not commercially sold in Canada.

INSPIOLTO RESPIMAT

Please consult the Product Monograph at www.boehringer-ingelheim.ca/sites/ca/files/documents/inspioltorespimatpmen.pdf for important information about:

- Contraindications in patients with hypersensitivity to tiotropium bromide monohydrate or olodaterol hydrochloride and patients with a history of hypersensitivity to atropine or its derivatives. All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication. INSPIOLTO RESPIMAT is not indicated for the treatment of asthma.
- The most serious warning and precaution regarding asthma-related death: Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. This was shown in a salmeterol study and is considered a class effect of LABA.
- Other relevant warnings and precautions regarding INSPIOLTO RESPIMAT: Should not be used more than once daily, should not be used in asthma, should not be used for treatment of acute episodes of bronchospasm, should not be initiated in patients with acutely deteriorating COPD, should not be used in conjunction with other long-acting beta$_2$-adrenergic agonists or short or long-acting muscarinic antagonists or at higher doses than recommended, patients with narrow-angle glaucoma or urinary retention or cardiovascular disorders, patients predisposed to low levels of serum potassium, patients with known history of QTc prolongation, risk factors for torsade de pointes or patients taking medications known to prolong the QTc interval, patients with convulsive disorders or thyrotoxicosis and patients who are unusually responsive to sympathomimetic amines, pre-existing diabetes mellitus or ketoacidosis, occurrence of dizziness or blurred vision may influence ability to use machinery, cardiovascular effects such as increase in pulse rate, systolic or diastolic blood pressure or cardiac arrhythmias, contains benzalkonium chloride which may cause wheezing and breathing difficulties (bronchospasm) especially in asthma patients, paradoxical bronchospasm that may be life-threatening, pregnant and nursing women.
- Conditions of clinical use, adverse reactions, drug interactions and dosing instructions.

The Product Monograph is also available by calling us at 1 (800) 263-5103 Ext. 84633.

SPIRIVA RESPIMAT

Please consult the Product Monograph at www.boehringer-ingelheim.ca/sites/ca/files/documents/spirivarespimatpmen.pdf for important information about:

- Contraindications in patients with a history of hypersensitivity to atropine or its derivatives (e.g. ipratropium).
- Relevant warnings and precautions regarding SPIRIVA RESPIMAT: Should not be used for initial treatment of acute episodes of bronchospasm or for the relief of acute symptoms; should not be initiated in patients with acutely deteriorating COPD; should not be used as a first-line treatment or monotherapy for asthma; immediate hypersensitivity reactions; should not be used more frequently than two inhalations once daily; patients with narrow-angle glaucoma, urinary retention (prostatic hyperplasia or bladder-neck obstruction); avoid getting mist into eyes; should not be used with other medicine containing a short or long-acting muscarinic antagonist; occurrence of dizziness or blurred vision may influence ability to drive and use machinery; cardiovascular effects, such as cardiac arrhythmias (e.g. atrial fibrillation and tachycardia), may be seen after the administration of muscarinic receptor antagonists; patients with moderate to severe renal impairment; contains benzalkonium chloride which may cause wheezing and breathing difficulties (bronchospasm) especially in asthma patients, inhalation-induced bronchospasm; pregnant and nursing women.
- Conditions of clinical use, adverse reactions, drug interactions and dosing instructions.

The Product Monograph is also available by calling us at 1 (800) 263-5103 Ext. 84633.

SPIRIVA HANDIHALER

Please consult the Product Monograph at www.boehringer-ingelheim.ca/sites/ca/files/documents/spirivapmen.pdf for conditions of clinical use, contraindications, warnings, precautions, adverse reactions, interactions and dosing. The Product Monograph is also available by calling us at 1 (800) 263-5103 Ext. 84633.

STRIVERDI RESPIMAT

Please consult the Product Monograph at www.boehringer-ingelheim.ca/sites/ca/files/documents/striverdipmen.pdf for important information about:

- Contraindications in patients with asthma without use of a long-term asthma control medication. STRIVERDI RESPIMAT is not indicated for the treatment of asthma.
- Most serious warnings and precautions regarding asthma-related death, STRIVERDI RESPIMAT is not indicated for the treatment of asthma.
- Other relevant warnings and precautions regarding regular use of short-acting bronchodilators: Should not be used in asthma, acute episodes of bronchospasm, patients with acutely deteriorating COPD, contains benzalkonium chloride which may cause wheezing and breathing difficulties (bronchospasm) especially in asthma patients, should not be used more often, or at higher doses than recommended, or with other LABA, caution in patients with cardiovascular disorders, cardiovascular effects (including increases in pulse rate and systolic/diastolic blood pressure, and/or symptoms), significant hypokalemia, caution in patients with convulsive disorders or thyrotoxicosis and patients who are unusually responsive to sympathomimetic amines, increases in plasma glucose (hyperglycemia), paradoxical bronchospasm, immediate hypersensitivity reactions, labour, patients with renal impairment, patients with known/suspected prolongation of QT interval, or taking medications known to prolong QTc interval and patients with pre-existing diabetes mellitus and ketoacidosis.
- Conditions of clinical use, adverse reactions, interactions and dosing instructions.

The Product Monograph is also available by calling us at 1 (800) 263-5103 Ext. 84633.

References: 1. Data on file. Boehringer Ingelheim (Canada) Ltd. September 24, 2019. **2.** Data on file. Boehringer Ingelheim (Canada) Ltd. November 28, 2017. **3.** INSPIOLTO® RESPIMAT® Product Monograph. Boehringer Ingelheim (Canada) Ltd. November 14, 2019. **4.** Data on file. Boehringer Ingelheim (Canada) Ltd. June 5, 2018. **5.** Data on file. Boehringer Ingelheim (Canada) Ltd. July 11, 2017. **6.** SPIRIVA® RESPIMAT® Product Monograph. Boehringer Ingelheim (Canada) Ltd. May 7, 2019. **7.** SPIRIVA® Product Monograph. Boehringer Ingelheim (Canada) Ltd. November 24, 2017. **8.** Buhl R, Maltais F, Abrahams R *et al*. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2–4). *Eur Resp J* 2015;45(4):969-979. **9.** Data on file. Boehringer Ingelheim (Canada) Ltd. June 20, 2019. **10.** Beeh K-M, Westerman J, Kirsten A-M *et al*. The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease. *Pul Pharm & Therap* 2015;32:53-59. **11.** O'Donnell DE, Casaburi R, Frith P *et al*. Effects of combined tiotropium/olodaterol on inspiratory capacity and exercise endurance in COPD. *Eur Respir J* 2017;49(4):1601348. **12.** Maltais F, O'Donnell D, Iturri JBG *et al*. Effect of 12 weeks of once-daily tiotropium/olodaterol on exercise endurance during constant work-rate cycling and endurance shuttle walking in chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2018;12:1-13. **13.** Singh D, Ferguson GT, Bolitschek J *et al*. Tiotropium+olodaterol shows clinically meaningful improvements in quality of life. *Resp Med* 2015;109(10):1312-1319. **14.** Beeh K-M, Derom E, Echave-Sustaeta J *et al*. The lung function profile of once-daily tiotropium and olodaterol via Respimat® is superior to that of twice-daily salmeterol and fluticasone propionate via Accuhaler® (ENERGITO® study). *Int J of COPD* 2016;11:193-205. **15.** Troosters T *et al*. Effect of bronchodilation and exercise training with behavior modification on exercise tolerance and downstream effects on symptoms and physical activity in COPD. *Am J Respir Crit Care Med* 2018;198(8):1021-1032. **16.** Calverley P, Anzueto A, Carter K *et al*. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomized, parallel-group, active-controlled trial. *Lancet Resp Med* 2018;6(5):337-344. **17.** Maltais F *et al*. Dual bronchodilation with tiotropium/olodaterol further reduces activity-related breathlessness versus tiotropium alone in COPD. *Eur Resp J* 2019;53:1-11. **18.** STRIVERDI® RESPIMAT® Product Monograph. Boehringer Ingelheim (Canada) Ltd. May 13, 2019.

Boehringer Ingelheim

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