Common Drug Review
Pharmacoeconomic Review Report

December 2015

Drug	Tiotropium bromide monohydrate and olodaterol hydrochloride (Inspiolto Respimat) for oral inhalation
Indication	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.
Listing request	For the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema, if the following clinical criteria are met: • moderate to severe COPD as defined by spirometry; • inadequate response to a long-acting beta$_2$ agonist (LABA) or long-acting muscarinic antagonist (LAMA).
Dosage form(s)	Inhalation solution delivered via the Respimat inhaler (2.5 mcg tiotropium and 2.5 mcg olodaterol per actuation)
NOC date	May 28, 2015
Manufacturer	Boehringer Ingelheim Canada Ltd.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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ABBREVIATIONS

ACL	aclidinium
BUD	budesonide
CDR	CADTH Common Drug Review
COPD	chronic obstructive pulmonary disease
FEV_1	forced expiratory volume in one second
FF	fluticasone furoate
FM	formoterol
FP	fluticasone propionate
GLY	glycopyrronium
ICS	inhaled corticosteroid
IND	indacaterol
LABA	long-acting $beta_2$ agonist
LAMA	long-acting muscarinic antagonist
OLO	olodaterol hydrochloride
SAL	salmeterol
TIO	tiotropium bromide monohydrate
UMEC	umeclidinium
VI	vilanterol

SUMMARY

Background

Inspiolto Respimat (tiotropium bromide monohydrate/olodaterol hydrochloride [TIO/OLO]) is a fixed-dose combination of a long-acting muscarinic antagonist (LAMA), tiotropium, and a long-acting beta$_2$ agonist (LABA), olodaterol, 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.[1] TIO/OLO is available as a multi-use cartridge to be used with the Respimat device, which provides 2.5 mcg of TIO and 2.5 mcg of OLO per actuation. The recommended dose of TIO/OLO is two actuations once daily ($2.10 daily).[1,2]

The manufacturer is requesting a listing as per the Health Canada–approved indication and in a similar manner to other fixed-dose combinations indacaterol plus glycopyrronium (IND/GLY)[3] and umeclidinium plus vilanterol (UMEC/VI):[4] for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema, if the following clinical criteria are met:

- moderate to severe COPD as defined by spirometry
- inadequate response to a long-acting bronchodilator (LABA) or long-acting anticholinergic.

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost comparison of TIO/OLO to other LAMA/LABA fixed-dose combinations, including IND/GLY, UMEC/VI, and aclidinium plus formoterol (ACL/FM), as well as inhaled corticosteroid (ICS) plus LABA fixed-dose combinations budesonide plus formoterol (BUD/FM), fluticasone furoate plus vilanterol (FF/VI), and fluticasone propionate plus salmeterol (FP/SAL) in patients with moderate to severe COPD over a one-year time frame, from the Canadian public payer perspective.[5]

For the comparison with other LAMA/LABA fixed-dose combinations (primary comparators), because no head-to-head trials were available, the assumption of similar efficacy and safety was based on a manufacturer-funded network meta-analysis comparing the effects of each drug in terms of change from baseline in trough forced expiratory volume in one second (FEV_1), Transitional Dyspnea Index focal score and proportion of responders, hospitalization, COPD exacerbations, health-related quality of life using the St. George's Respiratory Questionnaire, and discontinuations due to adverse events.[6] Results of the network meta-analysis suggested that TIO/OLO 5/5 mcg was not statistically significantly different from ACL/FM 400/12 mcg, IND/GLY 110/50 mcg, and UMEC/VI 62.5/25 mcg in lung function (through FEV_1), health-related quality of life, Transitional Dyspnea Index focal score, COPD exacerbations, and discontinuations due to adverse events.

The manufacturer did not provide evidence to support its assumption of similar efficacy and safety of TIO/OLO with ICS/LABA fixed-dose combinations in its pharmacoeconomic submission.[5] Although not referred to in the manufacturer's pharmacoeconomic analysis, as presented in the CADTH Common Drug Review (CDR) clinical report, results from ENERGITO[7] suggest that there is a greater improvement in FEV_1 outcomes with TIO/OLO 5/5 mcg compared with FP/SAL 500/50 mcg and FP/SAL 250/50 mcg, but the difference between TIO/OLO 5/5 mcg and the FP/SAL groups in trough FEV_1 did not exceed the clinically significant threshold of 0.10 L. However, it is uncertain what the minimal clinically important difference for LAMA/LABA versus ICS/LABA combination therapies should be.

The manufacturer assumed that all other aspects of patient management were equivalent for all comparators. As such, only drug acquisition costs were considered, which were primarily obtained from the Ontario Drug Benefit (April 2015). The Ontario Drug Benefit markup and dispensing fees were also incorporated to estimate the average annual cost per patient. For the base-case analysis, the unit price for IND/GLY was obtained from the Quebec Drug Formulary (April 2015), the price for UMEC/VI was from IMS Brogan DeltaPA, and the price of ACL/FM was not available at the time of the manufacturer's submission (see Table 4).

Key Limitations

- **Uncertain comparative effectiveness of TIO/OLO with other LAMA/LABA fixed-dose combinations:** As noted in Appendix 6 of the CDR clinical report, there was clinical heterogeneity among the studies included in the manufacturer-submitted network meta-analysis due to the inclusion of studies with outcomes measured at different time points in the same networks and differing inclusion criteria between included studies. Further, there was limited information provided as to how the various sources of heterogeneity were identified and accounted for in the network meta-analysis.
- **Uncertain comparative effectiveness of TIO/OLO versus ICS/LABA fixed-dose combinations:** The ENERGITO trial assessed only lung function; therefore, the comparative efficacy of TIO/OLO versus FP/SAL in terms of other relevant outcomes such as COPD exacerbations, hospitalizations, or quality of life is unknown. No evidence was provided to support the comparative efficacy and safety of TIO/OLO versus other ICS/LABAs fixed-dose combinations.
- **Exclusion of other relevant comparators:** The manufacturer did not consider various LABA or LAMA monotherapies that are less expensive than TIO/OLO. A stepwise approach to therapy is recommended for the treatment of COPD;[8,9] that is, TIO/OLO, like other combinations of a LABA and LAMA, should be considered in patients with COPD who remain symptomatic while using either a LAMA or a LABA. However, the approved indication for TIO/OLO includes the general population of COPD patients requiring bronchodilation therapy. Thus, the stepwise approach may not be followed in practice, and the drug could be used to replace a LAMA or a LABA monotherapy at increased cost.

Issues for Consideration

- At the submitted price, TIO/OLO is less costly than monotherapy with TIO using the HandiHaler device (Spiriva HandiHaler, $2.17 daily). Although Spiriva Respimat received a positive listing recommendation by the Canadian Drug Expert Committee in July 2015 and is less costly than Spiriva HandiHaler,[10] it was still not listed on most of CDR participating drug plans at the time of this review.
- In September 2015, the Canadian Drug Expert Committee recommended that ACL/FM be listed in a manner similar to other LAMA/LABA fixed-dose combination products and that drug plan costs for ACL/FM should not exceed drug plan costs for other listed LAMA/LABA combination products.[11]

Results and Conclusions

At the submitted price of $2.10 daily, TIO/OLO is less expensive than all other LAMA/LABA fixed-dose combinations (IND/GLY, $2.68 daily; UMEC/VI, $2.70 daily; and ACL/FM, $2.47 daily). TIO/OLO is also less costly than separately administered LAMA and LABA monotherapies (range, $3.26 to $3.85 daily), and ICS/LABA fixed-dose combinations (BUD/FM, $2.80 daily; FF/VI, $4.00 daily; FP/SAL, $3.25 to $4.61 daily).

TIO/OLO is more costly than most individual LAMA and LABA drugs.

Cost Comparison

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Costs of additional comparators are also presented in Appendix I.

TABLE 1: COST COMPARISON TABLE FOR BRONCHODILATOR THERAPIES FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug/Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Use	Daily Drug Cost ($)	Annual Cost ($)
Tiotropium plus olodaterol (Inspiolto Respimat)	**2.5/2.5 mcg**	**Inhalation solution**	**2.1000[a]**	**2.1000**	**5 mcg/5 mcg (2 actuations) once daily**	**2.10**	**766.50**
Other long-acting beta$_2$ agonist plus long-acting muscarinic antagonist fixed-dose combinations							
Indacaterol plus glycopyrronium (Ultibro Breezhaler)	110/50 mcg	Inhalant pwd capsule	2.6800	2.6800	110/50 mcg daily	2.68	978
Umeclidinium plus vilanterol (Anoro Ellipta)	62.5/25 mcg	Inhalant pwd (30 doses)	81.0000	2.7000	62.5/25 mcg daily	2.70	985.50
Aclidinium plus formoterol (Duaklir Genuair)	400/12 mcg	Inhalant pwd (60 doses)	74.1000[b]	1.2350	400/12 mcg twice daily	2.47	901.55
Inhaled corticosteroid plus long-acting beta$_2$ agonist fixed-dose combinations							
Budesonide plus formoterol (Symbicort Turbuhaler)	100/6 mcg 200/6 mcg	Inhalant pwd (120 doses)	64.5600 83.8800	0.5380 0.6990	400/12 mcg twice daily	2.80	1,021
Fluticasone furoate plus vilanterol trifenatate (Breo Ellipta)	100/25 mcg	Inhalant pwd (30 doses)	120.0000	4.0000	100/25 mcg once daily	4.00	1,460
Fluticasone propionate plus salmeterol (Advair Diskus)	100/50 mcg 250/50 mcg 500/50 mcg	Inhalant pwd (60 doses)	81.3929 97.4299 138.3141	1.3565 1.6238 2.3052	250/50 mcg or 500/50 mcg twice daily	3.25 to 4.61	1,186 to 1,683
Long-acting muscarinic antagonist							
Aclidinium bromide (Tudorza Genuair)	400 mcg	Inhalant pwd	53.1000	0.8850	400 mcg twice daily	1.77	646
Glycopyrronium bromide (Seebri)	50 mcg	Inhalant pwd	1.7700	1.7700	50 mcg daily	1.77	646

Drug/Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Use	Daily Drug Cost ($)	Annual Cost ($)
Tiotropium (Spiriva)	18 mcg	Inhalant pwd capsule	2.1667	2.1667	18 mcg daily	2.17	791
Tiotropium (Spiriva Respimat)	2.5 mcg	Inhalant solution	NA[c]	NA	2.5 mcg twice daily	NA	NA
Umeclidinium (Incruse Ellipta)	62.5 mcg	Inhalant pwd	NA[c]	NA	62.5 mcg once daily	NA	NA
Long-acting beta agonists							
Salmeterol (SereVent)	50 mcg	Inhalant pwd (60 doses)	56.1000	0.9400	50 mcg twice daily	1.87	683
Formoterol (Foradil)	12 mcg	Inhalant pwd capsule	0.8181[d]	0.8181	12 mcg to 24 mcg twice daily	1.64 to 3.27	597 to 1,194
Indacaterol maleate (Onbrez)	75 mcg	Inhalant pwd capsule	1.5500	1.5500	75 mcg daily	1.55	566

CDEC = CADTH Canadian Drug Expert Committee; NA = not available; pwd = powder.
[a] Manufacturer's submission price.
[b] CDEC recommendation for aclidinium/formoterol (Duaklir Genuair), September 2015.[11]
[c] Not listed by any of the CDR participating drug plans and no publicly available price at the time of the review.
[d] Alberta Health Drug Benefit List (August 2015).[12]
Source: Ontario Drug Benefit Formulary (August 2015)[13] unless otherwise stated.

APPENDIX 1: COSTS OF ADDITIONAL COMPARATORS

TABLE 2: COSTS OF ADDITIONAL COMPARATORS FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug/Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Use	Daily Drug Cost ($)	Annual Drug Cost ($)
Short-acting anticholinergic							
Ipratropium bromide (Atrovent)	20 mcg	MDI (200 doses)	18.9200	0.09	2 × 20 mcg 3 to 4 times daily	0.57 to 0.76	207 to 276
Short-acting beta$_2$ agonist							
Salbutamol (Airomir)	100 mcg	MDI (200 doses)	5.0000	0.02	100 mcg to 200 mcg up to 4 times daily	0.10 to 0.20	36 to 73
Salbutamol (Ventolin, generics)	100 mcg	Inhalant pwd (200 doses)	5.0000	0.02	100 mcg to 200 mcg up to 4 times daily	0.10 to 0.20	36 to 73
Terbutaline (Bricanyl Turbohaler)	0.5 mg	Inhalant pwd (100 doses)	7.7300	0.08	0.5 mg up to 6 times daily	0.08 to 0.46	28 to 167
Xanthine bronchodilator							
Theophylline (Uniphyl, generic)	400 mg 600 mg	SR tab SR tab	0.3734 0.4524	0.37 0.45	Once daily, generally 400 to 800 mg (varies with patient's lean muscle mass)	0.37 to 0.74	135 to 270
Phosphodiesterase type 4 inhibitor							
Roflumilast	500 mcg	tab	NA	NA	500 mcg daily	NA	NA

MDI = metered dose inhaler; NA = not available; pwd = powder; SR tab = sustained-release tablet.
Source: Ontario Drug Benefit Formulary (August 2015).[13]

APPENDIX 2: REVIEWER WORKSHEETS

TABLE 3: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug Product	TIO/OLO (Inspiolto Respimat) 5/5 mcg administered as two actuations of 2.5/2.5 mcg
Treatment	5/5 mcg once daily
Comparators	Primary comparators: LAMA/LABA fixed-dose combinations • IND/GLY 110/50 mcg • UMEC/VI 62.5/25 mcg • ACL/FM 400/12 mcg Secondary comparators: ICS/LABA fixed-dose combinations • BUD/FM 200/6 mcg • FF/VI 100/25 mcg • FP/SAL 250/50mcg and 500/50mcg
Study Question	What is the pharmacoeconomic impact of TIO/OLO compared with other LAMA/LABA combination therapies for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and for the reduction of exacerbations, from the perspective of a Canadian public payer?
Type of Economic Evaluation	Cost comparison (drug cost only)
Target Population	Patients with COPD, including chronic bronchitis and emphysema
Perspective	Canadian public payer
Outcomes Considered	Change in trough FEV_1 from baseline TDI focal score and proportion of responders Hospitalizations COPD exacerbations Discontinuations Health-related quality of life using the SGRQ
Key Data Sources	
Cost	Ontario Drug Benefit, Quebec Drug Formulary, and IMS Brogan DeltaPA
Clinical Efficacy	Manufacturer-conducted network meta-analysis
Harms	Manufacturer-conducted network meta-analysis
Time Horizon	One year
Results for Base Case	Inspiolto provides a cost-saving treatment option, up to $236.52 (with markup and dispensing fee included) per year relative to LAMA/LABA combinations and up to $989.63 per year relative to ICS/LABA combinations.

ACL = aclidinium; BUD= budesonide; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FM = formoterol; FP = fluticasone propionate; GLY = glycopyrronium; ICS = inhaled corticosteroid; IND = indacaterol; LABA = long-acting $beta_2$ agonist; LAMA = long-acting muscarinic antagonist; OLO = olodaterol; SAL = salmeterol; SGRQ = St. George's Respiratory Questionnaire; TDI = Transitional Dyspnea Index; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.

Manufacturer's Results

At the manufacturer-submitted price of $2.10 per day, the anticipated drug cost (including markup and dispensing fee) of tiotropium bromide monohydrate plus olodaterol hydrochloride (TIO/OLO) is $935.25 per patient per year. TIO/OLO is less costly than the other long-acting beta$_2$ agonist plus long-acting muscarinic antagonist (LABA/LAMA) fixed-dose combinations and the inhaled corticosteroid (ICS) plus LABA fixed-dose combinations (see Table 4), leading to cost savings (including markup and dispensing fees) of $228.64 and $236.52 per patient per year compared with indacaterol plus glycopyrronium (IND/GLY) and umeclidinium plus vilanterol (UMEC/VI), respectively. Relative to the various ICS/LABA combinations, the cost savings increase to $274.36 to $989.63 per patient per year.

The manufacturer conducted sensitivity analyses with increased number of days per claim (from 30 days to 90 days) and with markup and dispensing fee excluded from costs. The sensitivity analyses were very similar to the base-case results.

TABLE 4: MANUFACTURER'S COST ANALYSIS

Drug/Comparator	Strength	Recommended Use	Price/ Dose ($)	Daily Drug Cost ($)	Annual Drug Cost ($)[a,b]	Annual Cost Differential (Savings) with TIO/OLO ($)
TIO/OLO	5/5 mcg	5/5 mcg (2 actuations) once daily	2.1000[c]	2.1000	935.25	Reference
Primary Comparators: LABA/LAMA Fixed-Dose Combinations						
IND/GLY	110/50 mcg	110/50 mcg once daily	2.6800[d]	2.6800	1,163.89	(228.64)
UMEC/VI	62.5/25 mcg	62.5/25 mcg once daily	2.7000[e]	2.7000	1,171.77	(236.52)
ACL/FM	400/12 mcg	400/12 mcg twice daily	NA	NA	NA	NA
Secondary Comparators: ICS/LABA Fixed-Dose Combinations						
BUD/FM	200/6 mcg	400/12 mcg twice daily	0.6990	2.7960	1,209.61	(274.36)
FF/VI	100/25 mcg	100/25 mcg once daily	4.0000	4.0000	1,684.23	(748.98)
FP/SAL	250/50 mcg 500/50 mcg	250/50 mcg or 500/50 mcg twice daily	1.6238 2.3052	3.2477 4.6105	1,387.66 1,924.88	(452.41) (989.63)

ACL = aclidinium; BUD= budesonide; FF = fluticasone furoate; FM = formoterol; FP = fluticasone propionate; GLY = glycopyrronium; IND = indacaterol; NA = not available; OLO = olodaterol; SAL = salmeterol; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.

[a] Based on Ontario Drug Benefit rules of 8% markup and $8.83 dispensing fee. Prices are from the Ontario Drug Benefit Formulary (April 2015)[13] unless otherwise stated.

[b] Assumes a 30-days claim.

[c] Manufacturer's submission price.

[d] Quebec Drug Formulary (April 2015).[14]

[e] IMS Brogan DeltaPA.

Source: Adapted from the manufacturer's pharmacoeconomic submission, tables 1 and 2.[5]

CADTH Common Drug Review Results

The manufacturer had included the Ontario Drug Benefit markup and dispensing fees in its base-case analysis, which resulted in greater cost differentials when comparing different drugs. Due to variation in markup and dispensing fees across Canada, the CADTH Common Drug Review (CDR) considered only drug costs in its reanalyses.

Based on the prices obtained from the Ontario Drug Benefit (August 2015) as well as the September 2015 Canadian Drug Expert Committee (CDEC) recommendation for aclidinium plus formoterol (ACL/FM),[11] CDR calculated the cost differential between TIO/OLO and its comparators. The results in Table 5: CADTH Common Drug Review Analysis indicate cost savings (excluding markup and dispensing fees) of $135.05, $211.70, and $219.00 per patient annually compared with ACL/FM, IND/GLY, and UMEC/VI, respectively. Relative to the ICS/LABA fixed-dose combinations, the cost savings range from $254.04 to $916.32 per patient annually.

TABLE 5: CADTH COMMON DRUG REVIEW ANALYSIS

Drug/Comparator	Strength	Recommended Use	Price/ Dose ($)	Daily Drug Cost ($)	Annual Drug Cost ($)	Annual Cost Differential ($) (Savings) with TIO/OLO
TIO/OLO	2.5/2.5 mcg	5/5 mcg (2 actuations) once daily	2.1000[a]	2.1000	766.50	Reference
Primary Comparators: LABA/LAMA Fixed-Dose Combinations						
IND/GLY	110/50 mcg	110/50 mcg once daily	2.6800	2.6800	978.20	(211.70)
UMEC/VI	62.5/25 mcg	62.5/25 mcg once daily	2.7000	2.7000	985.50	(219.00)
ACL/FM	400/12 mcg	400/12 mcg twice daily	1.2350[b]	2.4700	901.55	(135.05)
Secondary Comparators: ICS/LABA Fixed-Dose Combinations						
BUD/FM	200/6 mcg	400/12 mcg twice daily	0.6990	2.7960	1,020.54	(254.04)
FF/VI	100/25 mcg	100/25 mcg once daily	4.0000	4.0000	1,460.00	(693.50)
FP/SAL	250/50 mcg 500/50 mcg	250/50 mcg or 500/50 mcg twice daily	1.6238 2.3052	3.2477 4.6105	1,185.40 1,682.82	(418.90) (916.32)

ACL = aclidinium; BUD= budesonide; CDEC = Canadian Drug Expert Committee; FF = fluticasone furoate; FM = formoterol; FP = fluticasone propionate; GLY = glycopyrronium; IND = indacaterol; OLO = olodaterol; SAL = salmeterol; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.

[a] Manufacturer's submission price.

[b] CDEC recommendation for ACL/FM (Duaklir Genuair), September 2015.[11]

Source: Ontario Drug Benefit Formulary (August 2015)[13] unless otherwise stated.

TABLE 6: KEY LIMITATIONS

Identified Limitation	Description	Implication
NMA's limitations	The studies included in the NMA were clinically heterogeneous with outcomes measured at different time points. Baseline characteristics across studies included in the NMA were not reported in detail, so it was unclear how these studies compared in terms of patient demographics, previous treatment history, smoking status, disease severity, and number of patients enrolled. No subgroup analyses were performed that would investigate any heterogeneity due to differences in baseline characteristics. The number of studies included in the NMA was not reported descriptively.	Although the NMA suggested that TIO/OLO was not statistically different from its comparators, the results of the NMA should be interpreted with caution.
Uncertain comparative effectiveness with ICS/LABA fixed-dose combinations	ICS/LABA combinations were excluded from the NMA. The only comparative data available are from the ENERGITO trial, which compared TIO/OLO with FP/SAL; however, the trial assessed only lung function. Other patient-relevant outcomes were not assessed.	There remains uncertainty about the comparative effectiveness of TIO/OLO with ICS/LABA fixed-dose combinations.
Relevant comparators were omitted	The manufacturer did not consider various LABA or LAMA monotherapies that are less expensive than TIO/OLO. As the approved indication for TIO/OLO includes the general population of COPD patients requiring bronchodilation therapy, the stepwise approach to therapy for the treatment of COPD may not be followed in practice.	TIO/OLO could be used to replace a LAMA or a LABA monotherapy at increased costs.

COPD = chronic obstructive pulmonary disease; FP = fluticasone propionate; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$ agonist; LAMA = long-acting muscarinic antagonist; NMA = network meta-analysis; OLO = olodaterol; SAL = salmeterol; TIO = tiotropium.

REFERENCES

1. [Pr]Inspiolto™ Respimat® (tiotropium (as tiotropium bromide monohydrate) and olodaterol (as olodaterol hydrochloride) inhalation solution): 2.5 mcg/2.5 mcg per actuation, and administration [product monograph]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd.; 2015 May 28.
2. CDR submission: Inspiolto™ Respimat® (Fixed Dose Combination (FDC) tiotropium and olodaterol), 2.5 mcg/2.5 mcg per actuation Inhalation Solution. Company: Boehringer Ingelheim (Canada), Ltd. [**CONFIDENTIAL** manufacturer's submission]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd/Ltee; 2015 Jun.
3. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: indacaterol/glycopyrronium (Ultibro Breezhaler - Novartis Pharmaceuticals Canada Inc.) Indication: Chronic Obstructive Pulmonary Disease [Internet]. Ottawa: CADTH; 2014 Nov. [cited 2015 Sep 24]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0369_Ultibro%20Breezhaler_Jan30_2015.pdf
4. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: umeclidinium bromide/vilanterol trifenatate (Anoro Ellipta — GlaxoSmithKline Inc.) Indication: Chronic Obstructive Pulmonary Disease [Internet]. Ottawa: CADTH; 2015 Jan. [cited 2015 Sep 24]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0371_Anoro_Ellipta_Jan-23-15.pdf
5. Pharmacoeconomic evaluation. In: CDR submission: Inspiolto™ Respimat® (Fixed Dose Combination (FDC) tiotropium and olodaterol), 2.5 mcg/2.5 mcg per actuation Inhalation Solution. Company: Boehringer Ingelheim (Canada), Ltd. [**CONFIDENTIAL** manufacturer's submission]. Burlington (ON): Boehringer Ingelheim (Canada), Ltd.; 2015 May.
6. Network meta-analysis for tiotropium + olodaterol fixed dose combination in chronic obstructive pulmonary disease (COPD): report. London (GB): IMS Health; 2015.
7. Clinical Trial Report 1237.11 Randomized, double-blind, double-dummy, active-controlled, 4 period complete cross-over study to compare the effect on lung function of 6 weeks once daily treatment with orally inhaled tiotropium+olodaterol fixed dose combination delivered by the Respimat® inhaler vs. 6 weeks twice daily treatment with fluticasone propionate+salmeterol fixed dose combination delivered by the Accuhaler® in patients with Chronic Obstructive Pulmonary Disease (COPD). [ENERGITO™]. Ingelheim am Rhein (GR): Boehringer Ingelheim International GmbH; 2015 Jun 26.
8. O'Donnell DE, Hernandez P, Kaplan A, Aaron S, Bourbeau J, Marciniuk D, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care. Can Respir J [Internet]. 2008 Jan [cited 2015 Jul 7];15 Suppl A:1A-8A. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2802325
9. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD [Internet]. London (UK): GOLD; 2014. [cited 2015 Jul 7]. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2014.pdf
10. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: tiotropium bromide (Spiriva Respimat — Boehringer Ingelheim Canada Ltd.) Indication: Chronic Obstructive Pulmonary Disease [Internet]. Ottawa: CADTH; 2015 Jul. [cited 2015 Sep 22]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0412-complete-Spiriva-Respimat-July-20-15-e.pdf
11. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: aclidinium/formoterol (Duaklir Genuair - AstraZeneca Canada Inc.) Indication: Chronic Obstructive Pulmonary Disease [Internet]. Ottawa: CADTH; 2015 Sep. [cited 2015 Sep 23]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0423_Duaklir_Genuair_Sept-22-15-e.pdf

12. Interactive drug benefit list [Internet]. Edmonton (AB): Alberta Health; 2015 Aug. [cited 2015 Sep 24]. Available from: https://idbl.ab.bluecross.ca/idbl/load.do

13. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index [Internet]. Toronto: The Ministry; 2015 Aug. [cited 2015 Sep 24]. Available from: https://www.healthinfo.moh.gov.on.ca/formulary/

14. List of medications [Internet]. Quebec (QC): Régie de l'assurance maladie du Quebec (RAMQ); 2015 Apr. [cited 2015 Sep 24]. Available from: https://www.prod.ramq.gouv.qc.ca/DPI/PO/Commun/PDF/Liste_Med/Liste_Med/liste_med_2015_03_16_en.pdf