



Common Drug Review

Pharmacoeconomic Review Report

July 2015

Drug	tiotropium bromide monohydrate (Spiriva Respimat) for 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/or emphysema, and for the reduction of exacerbations.
Listing request	As per indication, in a similar manner to Spiriva HandiHaler.
Manufacturer	Boehringer Ingelheim Canada Ltd.

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ABBREVIATIONS

CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	CADTH Common Drug Review
COPD	chronic obstructive pulmonary disease
ICS	inhaled corticosteroid
LABA	long-acting beta-2 agonist
LAMA	long-acting muscarinic antagonist
ODB	Ontario Drug Benefit
Tio H 18	tiotropium bromide dry powder inhalation device (Spiriva HandiHaler)
Tio R 5	tiotropium bromide Soft Mist Inhaler (Spiriva Respimat)

SUMMARY

1. BACKGROUND

Tiotropium bromide Soft Mist Inhaler (Spiriva Respimat; Tio R 5) is a long-acting muscarinic antagonist (LAMA) 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.¹ The manufacturer is requesting a listing in line with the indication. Tio R 5 is available as a multi-use cartridge containing 60 2.5 mcg actuations. As the recommended dose of Tio R 5 is two inhalations of 2.5 mcg (5 mcg) once daily, each cartridge provides a 30-day supply. At the confidentially submitted price of [REDACTED] per cartridge, Tio R 5 costs [REDACTED] daily.

2. SUMMARY OF THE ECONOMIC ANALYSIS SUBMITTED BY THE MANUFACTURER

The manufacturer submitted a cost-comparison analysis² considering Tio R 5 primarily with 18 mcg once-daily tiotropium bromide dry powder inhaler (Spiriva HandiHaler; Tio H 18) as well as with 50 mcg once-daily glycopyrronium (Seebri Breezhaler) and 400 mcg twice-daily acclidinium bromide (Tudorza Genuair), the other individual LAMA inhalers currently available in Canada. The perspective was that of a publicly funded Canadian drug plan with a time horizon of one year. Only drugs costs were included.

Ontario Drug Benefit (ODB) Formulary list prices (October 2014) were used to estimate comparator costs. Similar pharmacokinetic exposure, efficacy, and safety between Tio R 5 and Tio H 18 were assumed on the basis of two 4-week crossover trials³ and the long-term (2.3 years) TIOSPIR safety trial.⁴⁻⁶ No evidence was submitted regarding the clinical similarity between Tio R 5 and acclidinium bromide or between Tio R 5 and glycopyrronium.

The manufacturer concluded that Tio R 5 would lead to a savings of [REDACTED] per patient annually when compared with Tio H 18 when an 8% markup was included, or [REDACTED] without the markup. At the submitted price, Tio R 5 is [REDACTED] compared with the current ODB or Alberta Health list prices for glycopyrronium and acclidinium bromide.

3. KEY LIMITATIONS

3.1 Clinical Similarity to Some Comparators Uncertain

While head-to-head trials exist comparing the clinical efficacy⁷ and safety⁴⁻⁶ of Tio R 5 with Tio H 18, there are currently no trials available that compare Tio R 5 with glycopyrronium or acclidinium bromide. Mixed-treatment comparisons exist^{8,9} that compare Tio R 5 with other LAMAs as well as with long-acting beta-2 agonists (LABAs), inhaled corticosteroids (ICS)/LABA combinations, and placebo for outcomes of COPD exacerbations and mortality; however, limitations within these studies and the inconsistency of their results with those of the TIOSPIR trial suggest that the results should be interpreted with caution (see CADTH Common Drug Review [CDR] Clinical Report, Appendix 6). The clinical similarity of Tio R 5 to glycopyrronium and acclidinium bromide is uncertain; thus, whether Tio R 5 represents [REDACTED] treatment is also uncertain.

3.2 Appropriate Comparators Omitted

While the other LAMA products are the most direct comparators to Tio R 5, current COPD guidelines^{10,11} also recommend LABAs or ICS/LABAs as appropriate alternatives to LAMA therapy for some patients within the approved indication for Tio R 5. CDR compared the annual cost per patient of Tio R 5 with that of the available LABA and ICS/LABA products. At the submitted confidential price, Tio R 5 is less expensive than all ICS/LABA fixed-dose combinations, but more expensive than some LABA-only products (Table 3).

4. ISSUES FOR CONSIDERATION

4.1 Patients Requiring Double Therapy

While Tio R 5 is [REDACTED] compared with other single-drug LAMA inhalers for patients requiring^{10,11} a LAMA plus a LABA combination therapy, any combination of Tio R 5 with an individual LABA product is more expensive than the currently available LAMA/LABA combination inhalers (see TABLE 4).

4.2 Ease of Use/Device Preference

There is evidence that at least some patients using tiotropium bromide prefer the Respimat Soft Mist Inhaler to the HandiHaler dry powder device (see CDR Clinical Report, Appendix 7, for details).

4.3 Upcoming Comparators

While Tio R 5 is [REDACTED] compared with currently marketed LAMA inhalers for COPD, new LAMA products (e.g., umeclidinium bromide) are currently under review by CDR and the prices are currently not disclosed. Consequently, the relative cost of Tio R 5 to newly approved LAMAs is unknown.

5. RESULTS AND CONCLUSIONS

At the submitted confidential daily cost of [REDACTED], the use of Tio R 5 is less expensive per patient annually ([REDACTED] without markup) than the current list price of Tio H 18 and [REDACTED] glycopyrronium and aclidinium bromide. Tio R 5 is also less expensive than available ICS/LABA combination products, but is more expensive than some individual LABA products. For patients requiring LAMA plus LABA therapy, currently available LAMA/LABA fixed-dose combinations [REDACTED] possible combinations of Tio R 5 plus a LABA.

6. COST-COMPARISON TABLE

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. Additional drugs for COPD can be found in Appendix 2.

CDR PHARMACOECONOMIC REPORT FOR SPIRIVA RESPIMAT

TABLE 1: COST-COMPARISON TABLE FOR LAMAs, LABAs, AND COMBINATIONS FOR COPD

Drug/Comparator	Strength	Dosage Form	Price (\$)	Price/Dose (\$)	Recommended Daily Use	Daily Drug Cost (\$)	Average Annual Cost (\$)
Tiotropium Bromide (Spiriva Respimat)	2.5 mcg	Soft Mist Inhaler (60 doses)	██████ ^a	██████	5 mcg once daily	██████	██████
Other LAMAs							
Acclidinium bromide (Tudorza Genuair)	400 mcg	Inhalant pwd (60 doses)	53.1000	0.8850	400 mcg twice daily	1.77	646
Glycopyrronium bromide (Seebri)	50 mcg	Inhalant pwd capsule	1.7700	1.7700	50 mcg once daily	1.77	646
Tiotropium (Spiriva HandiHaler)	18 mcg	Inhalant pwd capsule	2.1667	2.1667	18 mcg once daily	2.17	791
LABAs							
Salmeterol (Serevent)	50 mcg	Inhalant pwd dose	0.9350	0.9350	50 mcg twice daily	1.87	683
Formoterol (Foradil)	12 mcg	Inhalant pwd capsule	0.8181	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 once daily	1.55	566
LABA/LAMA Combinations							
Indacaterol/ glycopyrronium (Ultibro Breezhaler)	110 mcg/50 mcg	Inhalant pwd capsule	2.6800 ^b	2.6800	110 mcg/50 mcg once daily	2.68	978
Umeclidinium/vilanterol (Anoro Ellipta)	62.5 mcg/25 mcg	Inhalant pwd (30 doses)	87.8900 ^{c,d}	2.9297	62.5 mcg/25 mcg once daily	2.93	1,069
ICS/LABA Combinations							
Budesonide/formoterol (Symbicort Turbuhaler)	100 mcg/6 mcg 200 mcg/6 mcg	Inhalant pwd (120 doses)	63.7920 82.8960	0.5316 0.6908	400 mcg/12 mcg twice daily	2.76	1,009
Fluticasone furoate/vilanterol trifenate (Breo Ellipta)	100 mcg/25 mcg	Inhalant pwd (30 doses)	120.0000 ^e	4.0000	100 mcg/25 mcg once daily	4.00	1,460
Fluticasone propionate/salmeterol (Advair Diskus)	100 mcg/50 mcg 250 mcg/50 mcg 500 mcg/50 mcg	Inhalant pwd (60 doses)	81.3900 97.4280 138.3120	1.3565 1.6238 2.3052	250 mcg/50 mcg or 500 mcg/50 mcg twice daily	3.25 to 4.61	1,186 to 1,684

CDR = CADTH Common Drug Review; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; LAMA = long-acting muscarinic antagonist; mcg = microgram; pwd = powder.

^a Manufacturer's confidential submission price.

^b Canadian Drug Expert Committee Final Recommendation for Ultibro Breezhaler.¹²

^c McKesson Canada wholesale price (February 2015).

^d Anoro Ellipta was recently reviewed by CDR; however, the confidential price was not made public.¹³

^e Ontario Drug Benefit (ODB) Formulary (March 2015).

Note: The LAMA umeclidinium (Incruse Ellipta) is currently under review by CDR; however, there is currently no publicly available price.

Source: Alberta Health Drug Benefit list (March 2015) unless otherwise stated.

APPENDIX 1: REVIEWER WORKSHEETS

1. Summary of Manufacturer’s Submission

Drug Product	Tiotropium bromide (Spiriva Respimat, Tio R 5)
Treatment	5 mcg tiotropium once daily
Comparator(s)	18 mcg HandiHaler once daily (Tio H 18) 50 mcg GLY once daily 400 mcg ACL twice daily
Study Question	
Type of Economic Evaluation	Cost-minimization analysis (considering only drug prices)
Target Population	Patients with COPD representing the population from the tiotropium Respimat trials and the approved indication
Perspective	Jurisdictional drug plan payer
Outcome(s) Considered	Drug costs
Key Data Sources	
Cost	ODB Formulary list price, including 8% markup and \$8.83 dispensing every 30 days in base case.
Clinical Efficacy	Head-to-head trials ⁷
Harms	TIOSPIR trial ⁴⁻⁶
Time Horizon	1 year
Results for Base Case	Tio R 5: ██████████ per patient per year Tio H 18: ██████████ per patient per year (\$156 more than Tio R 5) Tio R 5 is ██████████ GLY and ACL.

ACL = acclidinium bromide; COPD = chronic obstructive pulmonary disease; GLY = glycopyrronium; ODB = Ontario Drug Benefit; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose.

2. Manufacturer’s Results

The manufacturer submitted a cost comparison of drug prices over a one-year time horizon from the perspective of a public drug plan comparing Tio R 5 with Tio H 18 under the assumption of similar clinical efficacy and harms based on the results of two 4-week head-to-head efficacy trials⁷ as well as the large, long-term TIOSPIR safety trial.⁴⁻⁶ As secondary comparators, the manufacturer also compared Tio R 5 with glycopyrronium and with acclidinium, the other two LAMAs available in Canada. Drug costs were taken from the ODB Formulary with the exception of Tio R 5, the price of which was submitted confidentially by the manufacturer. An 8% markup was included and a dispensing fee of \$8.83 was assumed every 30 days. The manufacturer concluded that Tio R 5 was ██████████ to glycopyrronium and acclidinium bromide and would save ██████████ per patient annually compared with Tio H 18 (Table 2).

A sensitivity analysis considering only listed drug prices (i.e., without markup or dispensing fees) found that the use of Tio R 5 ██████████ per patient per year compared with Tio H 18.

TABLE 2: MANUFACTURER’S BASE-CASE RESULTS

Comparator	Cost per Day (\$)	Cost per Year (\$)	Incremental Cost Compared With Tio R 5 (\$)
Tio R 5, 5 mcg once daily (Spiriva Respimat)	█	█	NA
Tio H 18, 18 mcg once daily (Spiriva HandiHaler)	2.1667	962	█
Glycopyrronium, 50 mcg once daily (Seebri Breezhaler)	1.7700	805	█
Acclidinium bromide, 400 mcg twice daily (Tudorza Genuair)	1.7700	805	█

NA = not applicable; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
 Source: Manufacturer’s pharmacoeconomic submission, Tables 1 and 2.

3. CADTH Common Drug Review Results

While head-to-head trials exist comparing the clinical efficacy⁷ and safety⁴⁻⁶ of Tio R 5 with Tio H 18, there are currently no trials available that compare Tio R 5 with glycopyrronium or acclidinium bromide. Mixed-treatment comparisons exist^{8,9} that compare Tio R 5 with other LAMAs as well as LABAs, ICS/LABAs, and placebo in terms of COPD exacerbations or mortality; however, limitations of these studies and the inconsistency of their results with those of the TIOSPIR trial suggest that the results should be interpreted with caution (see CDR Clinical Report, Appendix 6). The clinical similarity of Tio R 5 to glycopyrronium and acclidinium bromide is less certain; thus, █ Tio R 5 to these comparators is also less certain.

While the other LAMA products are the most direct comparators to Tio R 5, current COPD guidelines^{10,11} also recommend LABAs or ICS/LABAs as appropriate alternatives to LAMA therapy for some portions of the patient population within Tio R 5’s approved indication. For example, the 2015 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend a LAMA or a LABA for patients with significant symptoms at low risk of exacerbations (Group B), a LAMA or an ICS/LABA for patients with few symptoms at high risk of exacerbation (Group C), and a LAMA and/or an ICS/LABA for patients with many symptoms and a high risk of exacerbation (Group D).

CDR compared the annual cost per patient of Tio R 5 with that of the available LABA and ICS/LABA products. Alberta Health’s list prices (without markup or fees) were used for the comparators rather than ODB Formulary prices, as Alberta Health reimburses more LABA-containing products for patients with COPD; LAMA list pricing was identical between ODB and Alberta Health in April 2015. At the submitted price, Tio R 5 is less expensive than all ICS/LABA fixed-dose combinations, but is more expensive than some LABA-only products (TABLE 3).

TABLE 3: CDR COMPARISON OF ANNUAL COST OF TIO R 5 WITH ANNUAL COSTS OF LABAs AND ICS/LABAs

Comparator	Cost per Day (\$)	Cost per Year (\$)	Incremental Cost Compared With Tio R 5 (\$)
Tio R 5, 5 mcg once daily (Spiriva Respimat)	█	█	Reference
LABAs			
Salmeterol (Serevent)	1.87	683	█
Formoterol (Foradil)	1.64 to 3.27	599 to 1,194	█ to █
Indacaterol maleate (Onbrez)	1.55	566	█

CDR PHARMACOECONOMIC REPORT FOR SPIRIVA RESPIMAT

Comparator	Cost per Day (\$)	Cost per Year (\$)	Incremental Cost Compared With Tio R 5 (\$)
ICS/LABAs			
Budesonide/ formoterol (Symbicort Turbuhaler)	2.76	1,007	██████
Fluticasone furoate/vilanterol trifenate (Breo Ellipta)	4.00	1,460	██████
Fluticasone propionate/salmeterol (Advair Diskus)	3.25 to 4.61	1,186 to 1,683	██████ to ██████

CDR = CADTH Common Drug Review; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; Tio R 5 = Spiriva Respimat 5 mcg daily dose.

Notes: Markups and dispensing fees not included. Prices are the Alberta Health Drug Benefit list prices (March 2015) with the exceptions of Tio R 5 (manufacturer's submitted price) and Breo Ellipta (ODB formulary).

According to current guidelines for the management of COPD, it is appropriate for some patients to be treated with a LAMA plus a LABA, or a LABA plus an ICS (e.g., alternate therapy choices for patients defined as Group B, C, or D by the 2015 GOLD guidelines¹¹).

As shown in TABLE 4, the cost (without markup or fees) of Tio R 5 in combination with the available LABA products ranges from ██████ to ██████ per patient per year, while the annual per-patient cost of the indacaterol/glycopyrronium and umeclidinium/vilanterol fixed-dose combination inhalers is \$978 and \$1,069, respectively. Thus, for patients requiring combination therapy with a LAMA plus a LABA, the available LABA/LAMA fixed-dose combinations ██████ all possible combinations that include Tio R 5. While not included in TABLE 4, the use of a LABA/LAMA fixed-dose combination rather than Tio R 5 plus an individual LABA would also save a dispensing fee every 30 to 90 days, depending on refill interval.

TABLE 4: COST OF TIO R 5 PLUS A LABA COMPARED WITH COSTS OF AVAILABLE LABA/LAMA FIXED-DOSE COMBINATIONS

Available Individual LABAs	LABA Cost per Day	LABA + Tio R 5 (██████) Cost per Day	LABA + Tio R 5 Cost per Year	Relative Cost Versus IND/GLY per Year (\$978)	Relative Cost Versus UME/VIL per Year (\$1,069)
Indacaterol 75 mcg once daily (Onbrez)	\$1.55	██████	██████	██████	██████
Formoterol 12 mcg twice daily (Foradil)	\$1.64	██████	██████	██████	██████
Salmeterol 50 mcg twice daily (Serevent)	\$1.87	██████	██████	██████	██████
Formoterol 24 mcg twice daily (Foradil)	\$3.27	██████	██████	██████	██████

IND/GLY = indacaterol/glycopyrronium 110/50 mcg daily (Ultibro Breezhaler); LABA = long-acting beta-2 agonist; LAMA = long-acting muscarinic antagonist; Tio R 5 = Spiriva Respimat 5 mcg daily dose; UME/VIL= umeclidinium/vilanterol 625/25 mcg daily (Anoro Ellipta).

Notes: This table is not intended to imply the clinical appropriateness or equivalence of any included combination. Markups and dispensing fees are not included.

4. Key Limitations

Identified Limitation	Description	Implication
Uncertainty in clinical similarity with some comparators	While head-to-head trials of Tio R 5 versus Tio H 18 exist, there are no head-to-head trials comparing Tio R 5 with the other LAMAs included in the manufacturer’s economic analysis.	Uncertainty in [REDACTED] to the health care system due to uncertain comparative efficacy and harms.
Some appropriate comparators excluded	According to GOLD 2014 and CTS 2007 clinical guidelines, it is appropriate to treat some patients in the approved indication with either a LAMA or a LABA (less severe COPD) or a LAMA or LABA + ICS. Thus, LABAs and LABA/ICS combination products are comparators for some portions of the indicated population. Additionally, patients with severe COPD are often treated with a LAMA plus a LABA; Tio R 5 as part of double therapy leads [REDACTED] total drug costs than some other combinations.	Tio R 5 is not less expensive than some LABA products, and when part of double or triple therapy leads [REDACTED] total drug costs than some other combinations. CDR conducted an analysis incorporating LABA products as well as one comparing Tio R 5 plus a LABA with available LAMA/LABA combinations.

CDR = CADTH Common Drug Review; COPD = chronic obstructive pulmonary disease; CTS = Canadian Thoracic Society; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; LAMA = long-acting anti-muscarinic antagonist; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose.

APPENDIX 2: ADDITIONAL COST COMPARATORS

TABLE 5: COSTS OF ADDITIONAL COMPARATORS FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug/ Comparator	Strength	Dosage Form	Price (\$)	Price/ Dose (\$)	Recommended Daily Use	Daily Drug Cost (\$)	Average Annual Cost (\$)
ICS							
Budesonide (Pulmicort Turbuhaler)	100 mcg	Inhalant pwd (200 doses)	31.1600	0.16	200 mcg to 400 mcg twice daily	0.64 to 0.93	233 to 339
	200 mcg		63.7200	0.32			
	400 mcg		93.0000	0.46			
Fluticasone propionate (Flovent Diskus, Flovent)	50 mcg	Inhalant pwd (60 doses)	15.1300 ^a	0.25	100 mcg to 500 mcg twice daily	0.80 to 2.75	291 to 1,004
	100 mcg		23.9300 ^a	0.40			
	250 mcg		41.2800	0.69			
	500 mcg	82.5400	1.38				
	50 mcg	Aerosol MDI (120 doses)	23.9300	0.20		0.80 to 2.75	291 to 1,004
125 mcg	41.2800		0.34				
250 mcg	82.5400	0.69					
Ciclesonide (Alvesco)	100 mcg	Solution aerosol (120 doses)	45.2160	0.38	100 mcg to 800 mcg once daily	0.38 to 2.49	138 to 910
	200 mcg		74.7600	0.62			
Short-acting muscarinic antagonist							
Ipratropium Bromide (Atrovent)	20 mcg	MDI (200 doses)	18.9200	0.09	2 x 20 mcg 3 to 4 times daily	0.57 to 0.76	207 to 276
SABA							
Salbutamol (Airomir)	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
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 (200 doses)	15.2800	0.08	0.5 mg up to 6 times daily	0.08 to 0.46	28 to 167
Xanthine Bronchodilator							
Theophylline (Uniphyll, generic)	100 mg	SR Tab	0.1300	0.13	Once daily, generally 400 mg to 800 mg (varies with patient's lean muscle mass)	0.50 to 1.00	184 to 367
	200 mg	SR Tab	0.1350	0.14			
	300 mg	SR Tab	0.1750	0.18			
	400 mg	SR Tab	0.5030	0.50			
600 mg	SR Tab	0.6090	0.61				

ICS = inhaled corticosteroid; MDI = metered dose inhaler; pwd = powder; SABA = short-acting beta-2 agonist.

^a Saskatchewan Drug Plan (February 2015).

Source: Alberta Health Formulary (February 2015), unless otherwise stated.

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