Common Drug Review
Pharmacoeconomic Review Report

August 2015

Drug	aclidinium bromide (Tudorza Genuair) (oral inhalation powder)
Indication	Long-term maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD), including bronchitis and emphysema.
Listing request	Listing in a manner similar to tiotropium bromide
Manufacturer	Almirall Canada Ltd.

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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

ACL	aclidinium bromide
CDR	CADTH Common Drug Review
COPD	chronic obstructive pulmonary disease
GLYB	glycopyrronium bromide
LAMA	long-acting muscarinic antagonist
TIO	tiotropium bromide

SUMMARY

Tudorza Genuair (aclidinium bromide [ACL]) is a long-acting muscarinic antagonist (LAMA) indicated for long-term maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. ACL is available as a 400 mcg powder in an inhaler containing 60 actuations. The manufacturer has submitted a confidential price of $[redacted] per inhaler or $[redacted] per day at the recommended dose of 400 mcg twice daily.

The manufacturer submitted a cost-minimization analysis in which ACL was compared with tiotropium bromide or glycopyrronium bromide. Indirect costs were assumed to be the same for the three drugs, except for the cost of secondary pharmacotherapy. Secondary pharmacotherapy was related to drug tolerability and was defined as the alternative COPD treatment that patients would use were they to discontinue the primary COPD treatment due to an adverse event. The manufacturer assumed that the tolerability of aclidinium bromide was better than that of both tiotropium bromide and glycopyrronium bromide. The results of the manufacturer's base case suggested that use of aclidinium bromide would result in annual cost savings to public drug plans of $[redacted] ([redacted]%) per patient compared with tiotropium bromide, or an annual incremental cost of $[redacted] ([redacted]%) per patient compared with glycopyrronium bromide.

The manufacturer's analysis had several limitations, the most significant of which was the assumption that aclidinium bromide had better tolerability than both tiotropium bromide and glycopyrronium bromide. This assumption was not supported by the manufacturer's indirect comparison of these treatments, which did not demonstrate any significant differences in tolerability or efficacy among aclidinium bromide, tiotropium bromide, and glycopyrronium bromide. Recalculations by CADTH of the cost of treatments, assuming no difference in tolerability among treatments, did not substantially alter the results: there was a cost saving of $86 (9.99%) for aclidinium bromide compared with tiotropium bromide, but a cost increase of $72 (10.4%) per patient compared with glycopyrronium bromide.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

Tudorza Genuair (aclidinium bromide [ACL]) is a long-acting muscarinic antagonist (LAMA) indicated as a long-term maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. ACL is available as 400 mcg powder for inhalation in an inhaler containing 60 actuations at a confidential price of $[redacted] ($[redacted] per day at the recommended dose of 400 mcg twice daily). An inhaler containing 30 actuations is available, but a price for this unit was not provided, as the manufacturer does not plan to market this in Canada, except to hospitals.

Cost Comparison Table

Clinical experts deemed the comparators presented in Table 1 to be appropriate comparators for ACL. Comparator treatments 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.

TABLE 1: COST COMPARISON OF ANTICHOLINERGIC DRUGS USED FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Drug / Comparator	Strength	Dosage Form	Price ($)	Price / Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Drug Cost ($)
Long-Acting Muscarinic Antagonist							
Aclidinium bromide (Tudorza Genuair)	**400 mcg**	**Inhalant pwd (60 doses)**	[redacted][a]	[redacted]	**400 mcg twice daily**	[redacted]	[redacted]
Glycopyrronium bromide (Seebri)	50 mcg	Inhalant pwd capsule	1.7700	1.77	50 mcg daily	1.77	646
Tiotropium bromide (Spiriva)	18 mcg	Inhalant pwd capsule	2.1667	2.17	18 mcg daily	2.17	791
Long-Acting Beta-2 Agonist + Inhaled Corticosteroid Combination							
Budesonide / Formoterol (Symbicort Turbuhaler)	100/6 mcg[b] 200/6 mcg	Inhalant pwd (120 doses)	63.2400 82.2000	0.53 0.69	400/12 mcg twice daily	2.74	1,000
Fluticasone / Salmeterol (Advair Diskus)	100/50 mcg[b] 250/50 mcg 500/50 mcg	Inhalant pwd (60 doses)	81.3929 97.4299 138.3141	1.36 1.62 2.31	250/50 mcg or 500/50 mcg twice daily	3.25–4.61	1,185–1,683
Mometasone / Formoterol[c] (Zenhale)	50/5 mcg 100/5 mcg 200/5 mcg	MDI (120 doses)	68.9000 87.4400 105.9800	0.57 0.73 0.88	100/10 mcg twice daily 200/10 mcg twice daily 400/10 mcg twice daily	2.30 2.91 3.53	838 1,064 1,289

MDI = metered dose inhaler; pwd = powder.
Source: Ontario Drug Benefit prices (October 2013) unless otherwise stated.
[a] Manufacturer's submission.[1]
[b] Based on the recommended daily dose, this strength cannot be used and was excluded from daily and annual drug cost.
[c] Saskatchewan Drug Plan (October 2013).
Note: Comparators listed are deemed the most appropriate; additional comparators are provided in APPENDIX 2.

2. SUMMARY OF PHARMACOECONOMIC SUBMISSION

The manufacturer's economic evaluation included a cost-minimization analysis. This analysis took the perspective of a publicly funded health care system and was conducted over a one-year time horizon; therefore, costs were not discounted. The cost-minimization analysis considered two comparators (from the same drug class, LAMA) as ACL; namely, tiotropium bromide (TIO) and glycopyrronium bromide (GLYB).

The costs of the comparators were obtained from a community pharmacy in Toronto for patients covered by the Ontario public drug program. The daily acquisition cost for ACL was $[redacted], while daily acquisition costs for TIO and GLYB were $2.17 and $1.77, respectively. Indirect costs were assumed to be the same for the three drugs, except for the cost of secondary pharmacotherapy. Secondary pharmacotherapy was related to drug tolerability and was defined as the alternative COPD treatment that patients would use were they to discontinue the primary COPD treatment due to an adverse event. The manufacturer assumed that the use of secondary pharmacotherapy would occur after the first month and would continue for the remaining 11 months of the treatment year. The secondary treatments for patients who used ACL as a primary treatment were Advair 250/50 ($3.19 per day) or Symbicort ($2.69 per day), whereas ACL was the secondary treatment for patients who used TIO and GLYB as a primary treatment. The combination therapy mometasone with formoterol (Zenhale) was not included as a secondary pharmacotherapy.

In the base case of the analysis provided by the manufacturer, the total undiscounted treatment cost per patient over a 12-month period was $[redacted] for ACL, $2,200 for TIO, and $2,051 for GLYB (see Table 2). These costs represent an annual incremental cost savings of $[redacted] ([redacted]%) when ACL is compared with TIO, and an annual incremental cost increase of $[redacted] ([redacted]%) when ACL is compared with GLYB (Table 2).

TABLE 2: COST PER PATIENT AND THE INCREMENTAL COSTS FOR 12 MONTHS OF THERAPY, BASED ON THE MANUFACTURER'S SUBMISSION

Base-case Analysis	Aclidinium	Tiotropium	Glycopyrronium
Drug acquisition	$[redacted]	$861	$702
Pharmacy dispensing fee	$100.80	$100.80	$100.80
Physician visits	$588.45	$588.45	$588.45
Laboratory evaluation	$507.22	$507.22	$507.22
Functional studies	$97.56	$97.56	$97.56
Secondary pharmacotherapy[a]	$39.45	$44.93	$54.56
Total cost[a]	**$[redacted]**	**$2,200**	**$2,051**
Incremental cost impact (saving) with aclidinium		**($[redacted])**	**$[redacted]**

Source: Manufacturer's submission.[1]

3. INTERPRETATIONS AND KEY LIMITATIONS

The following limitations with the manufacturer's analysis were noted.

3.1 Uncertainty Regarding Equivalence

The manufacturer stated that it assumed that there is similar efficacy and harms among ACL, TIO, and GLYB, based on the results of an indirect treatment comparison provided by the manufacturer.[1] However, whether this assumption is true is somewhat uncertain due to limitations with the indirect comparison, including a lack of a clear rationale for the exclusion of certain evidence (specifically, direct evidence for ACL versus TIO);[2-4] a lack of exploration of the effect of confounders such as the inclusion of trials in which concomitant medications were used; and heterogeneity in COPD severity and the duration of included studies.

3.2 Inappropriate Economic Analysis

Despite assuming similar efficacy and harms among ACL, TIO, and GLYB, the manufacturer's analysis included the costs associated with secondary pharmacotherapy following discontinuation of the primary therapy due to intolerable side effects; this implied a difference in tolerability among the primary therapies, which violated the assumption of similar harms. More specifically, the manufacturer assumed that ACL was more tolerable than the comparators. However, the available evidence does not support such an assumption (see Appendix 7 in the Clinical Review Report), and there do not appear to be any significant differences in tolerability or efficacy among ACL, TIO, and GLYB.

Furthermore, the manufacturer's calculations of costs for the secondary pharmacotherapy contained the following errors. First, the analysis assumed that if patients stopped using TIO or GLYB because of adverse events, the alternative treatment would be ACL. However, according to the clinical expert contracted by CADTH Common Drug Review (CDR) for the purpose of this review, this is incorrect, because a non-LAMA combination product should be used if ACL (a LAMA) is discontinued due to adverse events. Second, the model assumed that the use of the alternative treatments would occur after one month of treatment and would continue for at least 11 months. The manufacturer added the price of the secondary pharmacotherapy to annual costs based on the discontinuation rates due to adverse events for each therapy; however, it did not subtract the cost of the discontinued primary therapy to the total drug cost. Therefore, the manufacturer's model inflated total costs; this inflation affected the comparators, TIO and GLYB, more than ACL because of the higher rates of discontinuation attributed to the two comparators, creating a bias in favour of ACL.

To avoid the limitations noted above, CDR reviewers recalculated the base-case costs of treatments assuming no difference in the use (or cost) of secondary pharmacotherapy. The reanalysis considered only drug acquisition costs, because all other costs were assumed to be equal based on the results of the manufacturer's indirect comparison. The results of the CDR reanalysis were in line with the conclusion based on the manufacturer's results, that ACL presents cost savings versus TIO and is more costly than GLYB; however, the magnitude of the incremental costs (savings) in the CDR analysis differs:

- The incremental savings compared with TIO are less than the amount cited by the manufacturer ($[redacted] or [redacted]% in savings compared with $[redacted] or [redacted]% per patient).
- The additional costs compared with GLYB are greater than the amount cited by the manufacturer ($[redacted] or [redacted]% higher costs compared with $[redacted] or [redacted]% per patient).

4. ISSUES FOR CONSIDERATION

A price-reduction analysis carried out by CDR (APPENDIX 1) showed that the price of ACL would need to be reduced by [redacted]% to equal the lowest-priced alternative LAMA; namely, GLYB. At the lower price, ACL would generate annual cost savings of $[redacted] per patient compared with TIO.

5. CONCLUSIONS

At the confidential price, ACL is $[redacted] daily (400 mcg twice daily), which represents cost saving of $[redacted] ([redacted]%) per patient compared with TIO, but is $[redacted] ([redacted]%) per patient more costly than GLYB.

APPENDIX 1: PRICE-REDUCTION ANALYSIS

As ACL is more costly than GLYB in the base-case analysis, CDR calculated the price reduction that would be required so that the price of ACL would equal the price of the least expensive LAMA available, GLYB. As shown in Table 3, the price of ACL would need to be reduced by [redacted]% (from $[redacted] to $[redacted]) to be equivalent to the price of GLYB, which would then result in cost savings of $[redacted] and $[redacted] per patient per year compared with GLYB and TIO, respectively.

TABLE 3: CADTH COMMON DRUG REVIEW PRICE-REDUCTION ANALYSIS FOR ACLIDINIUM BROMIDE

Scenario	Current Price	Reduction Needed	Reduced Price	Savings[a] (min to max)	Max Savings[a]
Price reduction of ACL needed to equal GLYB	$[redacted]	[redacted]%	$[redacted]	$[redacted] to $[redacted]	$[redacted]
Price reduction of ACL needed to equal TIO		NA	NA	NA	NA

ACL = aclidinium bromide; GLYB = glycopyrronium bromide; NA = not applicable; TIO = tiotropium bromide.
[a] Savings per patient per year.

APPENDIX 2: COST COMPARISON TABLE – OTHER COMPARATORS

TABLE 4: COST COMPARISON – OTHER COMPARATORS

Drug / Comparator	Strength	Dosage Form	Price ($)	Price / Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Drug Cost ($)
Long-acting muscarinic antagonist							
Aclidinium bromide (Tudorza Genuair)	**400 mcg**	**Inhalant pwd (60 doses)**	[redacted][a]	[redacted]	**400 mcg twice daily**	[redacted]	[redacted]
Glycopyrronium bromide (Seebri)	50 mcg	Inhalant pwd capsule	1.7700	1.77	50 mcg daily	1.77	646
Tiotropium bromide (Spiriva)	18 mcg	Inhalant pwd capsule	2.1667	2.17	18 mcg daily	2.17	791
Long-acting beta-2 agonist							
Formoterol (Oxeze Turbuhaler)	6 mcg 12 mcg	Inhalant pwd (60 doses)	33.6500 44.8000	0.56 0.75	6 mcg to 12 mcg twice daily	1.12 to 1.49	409 to 545
Formoterol (Foradil)	12 mcg	Inhalant pwd (60 doses)	50.5300	0.84	12 mcg to 24 mcg twice daily	1.68 to 3.37	615 to 1,230
Indacaterol maleate (Onbrez)[a]	75 mcg	Inhalant pwd capsule	1.5500	1.55	75 mcg daily	1.55	566
Salmeterol (Serevent)	50 mcg	Inhalant pwd (60 doses)	56.1000	0.94	50 mcg twice daily	1.87	683
Inhaled corticosteroid							
Budesonide (Pulmicort Turbuhaler)	100 mcg 200 mcg 400 mcg	Inhalant pwd (200 doses)	31.2700 63.8600 112.6500	0.16 0.32 0.56	200 mcg to 400 mcg twice daily	0.64 to 1.13	233 to 411
Fluticasone (Flovent Diskus, Flovent)	50 mcg 100 mcg 250 mcg 500 mcg	Inhalant pwd (60 doses)	15.1300[b] 23.9300[b] 41.2800 82.5400	0.25 0.40 0.69 1.38	100 mcg to 500 mcg twice daily	0.80 to 2.75	291 to 1,004
	50 mcg 125 mcg 250 mcg	Aerosol MDI (120 doses)	23.9300 41.2800 82.5400	0.20 0.34 0.69		0.80 2.75	291 to 1,004
Ciclesonide (Alvesco)	100 mcg 200 mcg	Solution aerosol (120 doses)	45.5400 75.2800	0.38 0.63	100 mcg to 800 mcg once daily	0.38 to 2.51	139 to 916

Drug / Comparator	Strength	Dosage Form	Price ($)	Price / Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Drug Cost ($)
Long-acting beta-2 agonist plus inhaled corticosteroid combination							
Budesonide/ Formoterol (Symbicort Turbuhaler)	100/6 mcg[c] 200/6 mcg	Inhalant pwd (120 doses)	63.2400 82.2000	0.53 0.69	400/12 mcg twice daily	2.74	1,000
Fluticasone/ Salmeterol (Advair Diskus)	100/50 mcg[c] 250/50 mcg 500/50 mcg	Inhalant pwd (60 doses)	81.3929 97.4299 138.3141	1.36 1.62 2.31	250/50 mcg or 500/50 mcg twice daily	3.25 to 4.61	1,185 to 1,683
Mometasone / Formoterol[a] (Zenhale)	50/5 mcg 100/5 mcg 200/5 mcg	MDI (120 doses)	68.9000 87.4400 105.9800	0.57 0.73 0.88	100/10 mcg twice daily 200/10 mcg twice daily 400/10 mcg twice daily	2.30 2.91 3.53	838 1,064 1,289
Short-acting muscarinic antagonist							
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	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 4 times daily	0.10 to 0.20	36 to 73
Terbutaline (Bricanyl Turbuhaler)	0.5 mg	Inhalant pwd (200 doses)	7.64	0.04	0.5 mg up to 6 times daily	0.04 to 0.48	14 to 84
Xanthine bronchodilator							
Theophylline (Uniphyl, generic)	100 mg 200 mg 300 mg 400 mg 600 mg	SR Tab SR Tab SR Tab SR Tab SR Tab	0.1300[b] 0.0907[b] 0.1750 0.5030 0.6090	0.13 0.09 0.18 0.50 0.61	Once daily, generally 400 mg to 800 mg (varies with patient's lean muscle mass)	0.50 to 1.01	184 to 367

MDI = metered dose inhaler; pwd = powder; SR Tab = sustained release tablet.
Source: Ontario Drug Benefit prices (October 2013) unless otherwise stated.
[a] Manufacturer's submission[1] — confidential price.
[b] Saskatchewan Drug Plan (October 2013).
[c] Based on the recommended daily dose, this strength cannot be used and was excluded from daily and annual drug cost.

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