



# Common Drug Review

## *Pharmacoeconomic Review Report*

December 2014

<b>Drug</b>	indacaterol maleate/glycopyrronium bromide (Ultibro Breezhaler)
<b>Indication</b>	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.
<b>Listing request</b>	For the once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD (including chronic bronchitis and emphysema) who remain symptomatic despite use of monotherapy with a LABA or LAAC.
<b>Manufacturer</b>	Novartis Pharmaceuticals Canada Inc.

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## **ABBREVIATIONS**

<b>CDR</b>	CADTH Common Drug Review
<b>COPD</b>	chronic obstructive pulmonary disease
<b>FEV<sub>1</sub></b>	forced expiratory volume in one second
<b>ICS</b>	inhaled corticosteroid
<b>LAAC</b>	long-acting anticholinergic
<b>LABA</b>	long-acting beta-2 adrenergic agonist
<b>LAMA</b>	long-acting antimuscarinic agent

## **SUMMARY**

Ultibro Breezhaler (indacaterol 110 mcg + glycopyrronium 50 mcg) is a fixed combination product consisting of a long-acting beta-2 adrenergic agonist (LABA) and a long-acting antimuscarinic agent (LAMA, also referred to as a long-acting anticholinergic [LAAC] drug) that is 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. The manufacturer is seeking reimbursement for patients with COPD, including chronic bronchitis and emphysema, who remain symptomatic despite use of monotherapy with a LABA or a LAMA. Indacaterol 110 mcg + glycopyrronium 50 mcg is available as a capsule for inhalation at a price of \$2.68 per capsule (\$2.68 per day).

The manufacturer submitted a cost-minimization analysis comparing indacaterol + glycopyrronium with individually dosed formoterol and tiotropium, indacaterol and glycopyrronium (as their individual components), and a fluticasone propionate + salmeterol fixed combination product in adult patients with COPD who remain symptomatic despite monotherapy with a LABA or a LAMA. Comparable efficacy and safety was assumed between treatments based on head-to-head clinical trials.<sup>1-5</sup> CADTH Common Drug Review (CDR) calculations confirmed that indacaterol + glycopyrronium is less expensive than formoterol + tiotropium (\$3.66 per day), indacaterol and glycopyrronium (individual components, \$3.32 per day), and fluticasone propionate + salmeterol (\$3.25 to \$4.61 per day), and less expensive than all currently available LABA + LAMA combinations (range: \$3.26 to \$4.04 per day) and inhaled corticosteroid + LABA combination products (range: \$2.76 to \$4.61 per day). Indacaterol + glycopyrronium is, however, more expensive than monotherapy with a LABA (range: \$1.49 to \$1.87 per day) or a LAMA (\$1.77 to \$2.17 per day).

## REVIEW OF THE PHARMACOECONOMIC SUBMISSION

### 1. INTRODUCTION

Ultibro Breezhaler (indacaterol + glycopyrronium) is a combination product that consists of a long-acting beta-2 adrenergic agonist (LABA) and a long-acting antimuscarinic agent (LAMA) that is indicated for the long-term once-daily maintenance bronchodilator treatment of airway obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Indacaterol 110 mcg + glycopyrronium 50 mcg is available as a capsule for inhalation at a price of \$2.68 per capsule (\$2.68 per day).

#### 1.1 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.

**CDR PHARMACOECONOMIC REVIEW REPORT FOR ULTIBRO BREEZHALER**

**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 (\$)	Annual Cost (\$)
<b>Indacaterol + glycopyrronium (Ultibro Breezhaler)</b>	<b>110/50 mcg</b>	<b>Inhalant pwd capsule</b>	<b>2.6800<sup>a</sup></b>	<b>2.6800</b>	<b>110/50 mcg daily</b>	<b>2.68</b>	<b>978</b>
<b>LAMAs</b>							
Acclidinium bromide (Tudorza Genuair)	400 mcg	Inhalant pwd (60 doses)	53.1000 <sup>b</sup>	0.8850	400 mcg twice daily	1.77	646
Glycopyrronium bromide (Seebri)	50 mcg	Inhalant pwd capsule	1.7700	1.7700	50 mcg daily	1.77	646
Tiotropium (Spiriva)	18 mcg	Inhalant pwd capsule	2.1667	2.1667	18 mcg daily	2.17	791
<b>LABAs</b>							
Salmeterol (SereVent)	50 mcg	Inhalant pwd dose	0.9350	0.9400	50 mcg twice daily	1.87	683
Formoterol (Oxeze Turbuhaler)	6 mcg	Inhalant pwd (60 doses)	33.5280	0.5600	6 mcg to 12 mcg twice daily	1.12	408
	12 mcg		44.6700	0.7400		1.49	543
Formoterol (Foradil)	12 mcg	Inhalant pwd capsule	0.8181	0.8200	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
<b>Inhaled corticosteroid + LABA combinations</b>							
Budesonide + Formoterol (Symbicort Turbuhaler)	100/6 mcg	Inhalant pwd (120 doses)	63.7920	0.5316	400/12 mcg twice daily	2.76	1,009
	200/6 mcg		82.8960	0.6908			
Fluticasone furoate + Vilanterol trifenate (Breo Ellipta)	100/25 mcg	Inhalant pwd (30 doses)	130.2000 <sup>c</sup>	4.3400	100/25 mcg once daily	4.34	1,584
Fluticasone propionate + Salmeterol (Advair Diskus)	100/50 mcg	Inhalant pwd (60 doses)	81.3900	1.3565	250/50 mcg or 500/50 mcg twice daily	3.25 to 4.61	1,186 to 1,684
	250/50 mcg		97.4280	1.6238			
	500/50 mcg		138.3120	2.3052			

CDR = CADTH Common Drug Review; COPD = chronic obstructive pulmonary disease; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent; pwd = powder.

<sup>a</sup> Manufacturer's submission price.

<sup>b</sup> Ontario Drug Benefit Formulary (August 2014).

<sup>c</sup> McKesson Canada wholesale price (August 2014). Note that Breo Ellipta was recently reviewed by CDR; however, the confidential price was not made public:

[www.cadth.ca/media/cdr/complete/cdr\\_complete\\_breo\\_ellipta\\_august\\_20\\_2014.pdf](http://www.cadth.ca/media/cdr/complete/cdr_complete_breo_ellipta_august_20_2014.pdf).

Source: Alberta Health Drug Benefit List (Aug 2014) unless otherwise stated.

## 2. SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-minimization analysis with the perspective of the publicly funded health care system with a time horizon of one year. The target population consisted of adults with COPD who remain symptomatic despite use of monotherapy with a LABA or a LAMA. The use of rescue medication (e.g., short-acting beta-2 agonists), health care resource use due to adverse events, and additional direct and indirect costs associated with the treatment of COPD were all assumed to be similar between treatment groups and thus were not included in the analysis.

The use of a cost-minimization analysis was based on the results of three clinical trials.<sup>1-5</sup> Pharmaceutical costs were obtained from the Ontario Drug Benefit Formulary (November 2013) and the Ontario Drug Benefit mark-up and dispensing fee were applied every 90 days. The analysis compared indacaterol 110 mcg + glycopyrronium 50 mcg with formoterol 12 mcg twice daily and tiotropium 18 mcg once daily, indacaterol 75 mcg and glycopyrronium 50 mcg administered individually once daily, and fluticasone propionate 500 mcg + salmeterol 50 mcg combination product twice daily.

In the manufacturer’s analysis (see Table 2), the one-year cost of indacaterol + glycopyrronium (\$1,091) was \$421 less expensive than formoterol + tiotropium (\$1,513), \$287 less than indacaterol and glycopyrronium (as individual components) (\$1,379), and \$761 less than fluticasone propionate + salmeterol (\$1,855).

**TABLE 2: MANUFACTURER’S COST ANALYSIS RESULTS FOR ANNUAL COSTS OF INDACATEROL + GLYCOPYRRONIUM VERSUS COMPARATORS**

Comparator	Strength	Recommended Daily Use	Annual Drug Cost <sup>a</sup>	Annual Cost With Mark-Up/Fees <sup>a</sup>
Indacaterol + glycopyrronium <sup>b</sup>	110/50 mcg	110/50 mcg	\$978.20	\$1,091.41
Tiotropium + formoterol	18 mcg 12 mcg	18 mcg 24 mcg	\$1,335.91	\$1,512.70
Indacaterol and glycopyrronium (as individual components) <sup>b</sup>	75 mcg 50 mcg	75 mcg 50 mcg	\$1,211.80	\$1,378.66
Fluticasone propionate + salmeterol	500/50 mcg	1000/100 mcg	\$1,682.82	\$1,852.41

Source: Manufacturer’s Submission: Cost-analysis of Ultibro Breezhaler, Table 5.

<sup>a</sup> Indacaterol + glycopyrronium cost provided by manufacturer; other prices are from the Ontario Drug Benefit Formulary. Mark-up is 8%, and \$8.62 dispensing fee is applied to each prescription every 90 days.

<sup>b</sup> Indacaterol and glycopyrronium dosing (75+50 mcg) in this analysis is different from both the dosing of indacaterol + glycopyrronium (110/50 mcg) and the component dosing used in the clinical trial (150 + 50 mcg).

### 3. KEY LIMITATIONS

#### 3.1 Appropriate Comparators Were Omitted

The manufacturer compared indacaterol + glycopyrronium with indacaterol and glycopyrronium, formoterol and tiotropium, and fluticasone propionate + salmeterol in its economic analysis on the basis of head-to-head trials. Consultation by CDR with a clinical expert indicated that other combinations such as indacaterol and tiotropium or salmeterol and tiotropium are also commonly used for COPD patients requiring LABA and LAMA combination therapy. Neither direct nor indirect evidence is available comparing indacaterol + glycopyrronium with these or other combinations.

However, based on a comparison of drug costs alone (assuming clinical similarity between all LABA and LAMA combinations), indacaterol + glycopyrronium would lead to savings of \$280 to \$588 per patient per year relative to all combinations of currently available LABA and LAMA products when mark-ups and dispensing fees are incorporated (see Table 3). CDR used Alberta Health Drug Benefit List prices (with the exception of aclidinium bromide), mark-ups, and fees for its analyses, as Alberta Health does not restrict LABA use for COPD patients, unlike several other jurisdictions. If dispensing fees and mark-ups are not included, annual savings per patient range from \$211 to \$495 with indacaterol + glycopyrronium over combinations of available LABAs and LAMAs.

**TABLE 3: CDR ANALYSIS OF ANNUAL COSTS OF EACH AVAILABLE LAMA COMBINED WITH EACH AVAILABLE LABA**

IG 110/50 mcg daily \$1,112.84 <sup>a</sup> (ref)		Annual Costs (Incremental Cost Relative to IG) of LAMAs Plus Each LABA		
		Aclidinium Bromide <sup>b</sup> 400 mcg Twice Daily	Glycopyrronium Bromide 50 mcg Daily	Tiotropium 18 mcg Daily
Annual Costs (Incremental Cost Relative to IG) of LABAs + Each LAMA	Salmeterol 50 mcg twice daily	\$1,543.49 (\$431)	\$1,543.49 (\$431)	\$1,700.83 (\$588)
	Formoterol (Oxeze) 12 mcg twice daily	\$1,392.37 (\$280)	\$1,392.37 (\$280)	\$1,549.72 (\$437)
	Formoterol (Foradil) 12 mcg twice daily	\$1,450.76 (\$338)	\$1,450.76 (\$338)	\$1,608.10 (\$495)
	Indacaterol maleate 75 mcg daily	\$1,416.57 (\$304)	\$1,416.57 (\$304)	\$1,573.91 (\$461)

Costs were calculated using Alberta Health Drug Benefit List (Aug 2014) prices unless otherwise indicated. Markup was 8.665%, and a dispensing fee of \$12.30 was applied every 90 days for each product. This table is not intended to imply the clinical relevance or appropriateness of any combination of LABA and LAMA comparators.

IG = indacaterol + glycopyrronium; LABA = long-acting beta-2 adrenergic agonist; LAMA = long-acting antimuscarinic agent.

<sup>a</sup> Cost calculated from manufacturer's submitted price.

<sup>b</sup> Costs calculated using Ontario Drug Benefit Formulary list price.

Additionally, if fluticasone propionate + salmeterol is accepted as a valid comparator for indacaterol + glycopyrronium in patients not adequately responding to a LAMA or LABA alone (see Assumption of Clinical Equivalence section, below), then other inhaled corticosteroid (ICS) + LABA combinations such as budesonide + formoterol and fluticasone furoate + vilanterol could also be considered as economic comparators. Indacaterol + glycopyrronium is less expensive than all currently available ICS/LABA combinations (see Table 4, savings range: \$33 to \$766 annually per patient).

**TABLE 4: CDR ANALYSIS OF INDACATEROL + GLYCOPYRRONIUM ANNUAL COSTS AND RELATIVE SAVINGS VERSUS ICS+LABA COMBINATIONS**

Comparator	Strength	Recommended Daily Use	Annual Drug Cost	Annual Cost With Mark-Up/Fees <sup>a</sup>	Relative Cost Versus IG
IG <sup>b</sup>	110/50 mcg	110/50 mcg	\$978.20	\$1,112.84	Ref
Budesonide + formoterol <sup>c</sup>	200/6 mcg	400/12 mcg	\$1,008.57	\$1,145.84	\$33
Fluticasone furoate + vilanterol <sup>d</sup>	100/25 mcg	100/25 mcg	\$1,584.10	\$1,771.25	\$658
Fluticasone propionate + salmeterol <sup>c</sup>	250/50 mcg	500/100 mcg	\$1,185.37	\$1,337.97	\$225
	500/50 mcg	1000/100 mcg	\$1,682.80	\$1,878.49	\$766

CDR = CADTH Common Drug Review; IG = indacaterol + glycopyrronium; ICS = inhaled corticosteroid; LABA = long-acting beta-2 adrenergic agonist.

<sup>a</sup> Mark-up is 8.662%, and \$12.30 dispensing fee is applied to each prescription every 90 days.

<sup>b</sup> Cost calculated from manufacturer's submitted price

<sup>c</sup> Cost calculated from Alberta Health Benefit Formulary (August 2014)

<sup>d</sup> Cost calculated from McKesson Canada wholesale price (August 2014)

### 3.2 Unclear Cost-Effectiveness Relative to Monotherapy

While the manufacturer has requested a listing for COPD patients who remain symptomatic despite the monotherapy with a LABA or a LAMA, the approved indication includes the general population of COPD patients requiring bronchodilation therapy. Indacaterol + glycopyrronium showed statistically superior spirometry outcomes versus monotherapy with indacaterol, glycopyrronium, or tiotropium in the SHINE trial,<sup>6</sup> and two crossover studies<sup>7,8</sup> also demonstrated improved spirometry outcomes when indacaterol + glycopyrronium was compared with tiotropium. With evidence of the improved efficacy of indacaterol + glycopyrronium compared with monotherapy in terms of forced expiratory volume in one second (FEV<sub>1</sub>) (although not in terms of exacerbation rates), but at an increased cost, the cost-effectiveness of indacaterol + glycopyrronium compared with monotherapy with either LABAs or LAMAs is unknown in the absence of a cost-utility model.

### 3.3 Assumption of Clinical Equivalence

Indacaterol + glycopyrronium has been compared in clinical trials with the combination of its individual components, with the LABA plus LAMA combination of formoterol and tiotropium, and with the ICS/LABA fixed dose combination fluticasone propionate + salmeterol. Few differences were found between comparators for measured outcomes, and those that were found favoured indacaterol + glycopyrronium. However, limitations exist, particularly in terms of the study length and the dosing used in the trial comparing indacaterol + glycopyrronium with its individual components and in terms of the clinical relevance of comparing indacaterol + glycopyrronium with fluticasone propionate + salmeterol in a population at low risk of exacerbation.

- The manufacturer provided direct evidence to show that indacaterol + glycopyrronium is likely comparable, at least in the short term, to its individual components. The BEACON study<sup>1,2</sup> showed that indacaterol + glycopyrronium was non-inferior to 150 mcg indacaterol and 50 mcg glycopyrronium administered separately for trough FEV<sub>1</sub>, FEV<sub>1</sub> area under the curve from zero hours to four hours, symptom scores, reduction in need for rescue medication, and overall and serious adverse events. The evidence for this comparison is limited by the short duration of the trial (four weeks) and the differences in indacaterol dosing. The usual dose for indacaterol when used as an individual inhaler, as stated in the product monograph, is 75 mcg daily, which is the dosing assumed in both the manufacturer's cost-minimization analysis and CDR's reanalysis, while the indacaterol dose in the indacaterol + glycopyrronium combination product is 110 mcg, and the dose in comparator group of the BEACON trial was 150 mcg daily.
- Direct evidence showing that indacaterol + glycopyrronium may be considered comparable to combination therapy with another LABA and LAMA is also available. The QUANTIFY study<sup>3</sup> found statistically but not clinically significant improvement in pre-dose FEV<sub>1</sub> and forced vital capacity with indacaterol + glycopyrronium compared with formoterol and tiotropium, with similar quality of life, and rates of exacerbation and treatment-emergent adverse events between treatments.
- The manufacturer also submitted the ILLUMINATE trial,<sup>4,5</sup> which compared indacaterol + glycopyrronium with the ICS + LABA combination of fluticasone propionate 500 mcg + salmeterol 50 mcg twice daily. Significantly improved post-dose area under the curve from 0 to 12 hours was found in patients using indacaterol + glycopyrronium compared with fluticasone propionate + salmeterol, as well as significantly improved pre-dose FEV<sub>1</sub> and spirometry, Transition Dyspnea Index focal score and responder rate, and significantly decreased need for rescue medication, as well as a lower incidence of adverse events and pneumonia. However, ILLUMINATE did not report exacerbation outcomes and included patients with moderate to severe COPD who were at low risk of exacerbation, while current guidelines<sup>9,10</sup> recommend the use of ICS only in COPD patients at high risk of exacerbation. While it is likely that ICS/LABA combinations are often prescribed to patients with inadequate response to LABAs or LAMAs alone, regardless of exacerbation risk, this difference in population may limit the clinical relevance of the ILLUMINATE trial.

While there were limitations identified with the clinical trials, the results generally support that indacaterol + glycopyrronium is associated with at least similar benefits in trial outcomes compared with its individual components taken concomitantly, formoterol and tiotropium, and fluticasone propionate + salmeterol over the trial periods.

## **4. ISSUES FOR CONSIDERATION**

### **4.1 Patient Convenience and Adherence**

While there are little data to support the benefit of once-daily over twice-daily dosing for COPD medications, or one inhaler versus two, it is possible that patients will value or benefit from a decreased dosing schedule. Additionally, the availability of a LABA + LAMA combination product may decrease the prescription of ICS/LABA combinations in patients at lower risk of exacerbations.

### **4.2 Triple Therapy**

According to the 2014 Global Initiative for Chronic Obstructive Lung Disease<sup>9</sup> and the 2007 Canadian Thoracic Society<sup>10</sup> guidelines, it may be appropriate for some patients who have many symptoms and who are at high risk of exacerbations (i.e., Group D patients within the Global Initiative for Chronic Obstructive Lung Disease guidance and patients with severe impairment in that of the Canadian Thoracic Society) to receive triple therapy with an ICS, a LABA, and a LAMA. Costs for such patients will be higher than those on LABA + LAMA alone, but using indacaterol + glycopyrronium as part of a triple therapy regime is likely to reduce costs compared with combinations of currently available triple therapy components.

## **5. CONCLUSIONS**

At the submitted price of \$2.68 per 110/50 mcg capsule for inhalation (\$2.68 daily), indacaterol + glycopyrronium is less expensive than all available combinations of individual LABA and LAMA inhalers (range: \$3.26 to \$4.04 daily). If listed, and assuming equivalent efficacy and safety assumptions are valid, indacaterol + glycopyrronium would result in annual savings of \$280 to \$588 per patient when compared with currently available LABA + LAMA combinations. Indacaterol + glycopyrronium is also less expensive (range: \$33 to \$766 per patient per year) than the currently available ICS + LABA combination products, but \$203 to \$472 more expensive per patient per year than monotherapy with a LABA or a LAMA.

## APPENDIX 1: ADDITIONAL COMPARATOR COSTS

TABLE 5: COSTS OF ADDITIONAL COMPARATORS FOR THE TREATMENT OF COPD

Drug/Comparator	Strength	Dosage Form	Price (\$)	Price/ Dose (\$)	Recommended Daily Use	Daily Drug Cost (\$)	Annual Drug Cost (\$)
<b>ICS</b>							
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 <sup>a</sup>	0.25	100 mcg to 500 mcg twice daily	0.80 to 2.75	291 to 1,004
	100 mcg		23.9300 <sup>a</sup>	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			
<b>SAMA</b>							
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
<b>SABA</b>							
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 Turbuhaler)	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
<b>Xanthine Bronchodilator</b>							
Theophylline	100 mg	SR tab	0.1300	0.13	Once daily,	0.50 to 1.00	184 to 367

**CDR PHARMACOECONOMIC REVIEW REPORT FOR ULTIBRO BREEZHALER**

Drug/Comparator	Strength	Dosage Form	Price (\$)	Price/ Dose (\$)	Recommended Daily Use	Daily Drug Cost (\$)	Annual Drug Cost (\$)
(Uniphyll, generic)	200 mg 300 mg 400 mg 600 mg	SR tab SR tab SR tab SR tab	0.1350 0.1750 0.5030 0.6090	0.14 0.18 0.50 0.61	generally 400 to 800 mg (varies with patient's lean muscle mass)		

ICS = inhaled corticosteroid; MDI = metered-dose inhaler; pwd = powder; SABA = short-acting beta-2 adrenergic agonist; SAMA = short-acting antimuscarinic agent; SR tab = sustained release tablet.

<sup>a</sup> Saskatchewan Drug Plan (July 2014).

Source: Alberta Health Formulary (July 2014) unless otherwise stated.

## REFERENCES

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