Common Drug Review
Pharmacoeconomic Review Report

August 2015

Drug	alogliptin/metformin, fixed-dose combination (Kazano)
Indication	As an adjunct to diet and exercise in patients inadequately controlled on metformin or in patients already being treated with the combination of alogliptin and metformin
Listing request	As per indication under review
Manufacturer	Takeda Canada Inc.

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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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

A1C	glycated hemoglobin
CDR	CADTH Common Drug Review
DPP-4	dipeptidyl peptidase-4
FDC	fixed-dose combination
NMA	network meta-analysis
RCT	randomized controlled trial
T2DM	type 2 diabetes mellitus

SUMMARY

Background

Kazano (alogliptin/metformin) is a fixed-dose combination (FDC) of a selective inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme (alogliptin) plus the biguanide drug metformin. It is available as 12.5 mg/500 mg, 12.5 mg/850 mg, and 12.5 mg/1,000 mg tablets. The recommended dose of alogliptin/metformin FDC is 12.5 mg of alogliptin plus either 500 mg, 850 mg, or 1,000 mg of metformin to be taken twice daily. The manufacturer submitted a flat price of $1.37 per tablet ($2.74 per day).

Alogliptin/metformin FDC was shown to be bioequivalent to alogliptin + metformin co-administered as individual dosage forms in healthy patients, according to the European Medicines Agency (EMA) standards for bioequivalence.[1]

Upon submission, the manufacturer requested reimbursement in a manner equivalent to the other DPP-4 inhibitors currently available in Canada. Upon review of the draft CADTH Common Drug Review (CDR) clinical and pharmacoeconomic reports, the manufacturer asked that the requested listing criteria be modified to reflect the indication under review:

- As an adjunct to diet and exercise in patients inadequately controlled on metformin or in patients already being treated with the combination of alogliptin and metformin.

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost-minimization analysis[2] comparing alogliptin/metformin FDC (12.5 mg alogliptin/500 mg, 850 mg, or 1,000 mg metformin) with three other DPP-4 inhibitor/metformin FDCs available in Canada: linagliptin/metformin FDC (2.5 mg/500 mg; 2.5 mg/850 mg; 2.5 mg/1,000 mg), saxagliptin/metformin FDC (2.5 mg/500 mg; 2.5 mg/850 mg; 2.5 mg/1,000 mg), and sitagliptin/metformin FDC (50 mg/500 mg) for patients with type 2 diabetes mellitus (T2DM). Because no head-to-head trials were available comparing alogliptin/metformin with other DPP-4 inhibitor/metformin FDCs, the assumption of similar efficacy and safety was based on a manufacturer-funded network meta-analysis (NMA) that compared the effects of each drug in terms of glycated hemoglobin (A1C) change from baseline, the percentage of patients achieving target A1C < 7%, weight, and hypoglycemic events. The NMAs suggested that there are no differences among DPP-4 inhibitors either as monotherapy or combination therapy on A1C, body weight, and hypoglycemia.[2] The NMA by Tolley et al.[3] also suggested that alogliptin as dual therapy with either metformin or a sulfonylurea has a high probability of producing similar reductions in A1C (within a margin of 0.3%) as other DPP-4 inhibitors available in Canada.

The analysis was conducted from the Canadian public-payer perspective. Only drug acquisition costs were considered (not including markup). Because alogliptin, saxagliptin, linagliptin, and sitagliptin represent the same drug class (DPP-4 inhibitors), the manufacturer assumed all other aspects of patient management were equivalent (routine patient care and adverse events). For the base-case analysis, the unit drug prices were determined from the manufacturer (alogliptin/metformin FDC), from IMS Brogan price data (linagliptin/metformin FDC and saxagliptin/metformin FDC), and from Ontario Drug Formulary for sitagliptin/metformin FDC.[2] In sensitivity analyses, a cost comparison was conducted between alogliptin/metformin FDC and other classes of oral T2DM drugs in combination with metformin, as fixed- and non-fixed-dose combinations with metformin: sulfonylureas, thiazolidinediones (TZDs), and DPP-4 inhibitors.

Key Limitations

- **Limitations With the Network Meta-analysis:** There was heterogeneity among randomized controlled trials (RCTs) included in the NMA in baseline characteristics and study durations. The primary outcome in most studies was change in A1C from baseline; thus it remains unclear whether the outcomes for body weight and hypoglycemic events were adequately powered in the respective studies to detect meaningful differences. A limitation of the Craddy et al. NMA[4] was the pooling of studies of various sulfonylureas, a likely source of heterogeneity. A key limitation of the Craddy et al. NMA[4] was the conclusion of similar numerical efficacy between DPP-4 inhibitors based on the overlap in the 95% credible intervals for the treatment effects. However, the subsequent NMA by Tolley et al. (2014)[3] suggested that there are no differences across DPP-4 inhibitors on A1C, body weight, and hypoglycemia, and that alogliptin as dual therapy with either metformin or sulfonylurea has a high probability of producing similar reductions in A1C (within a margin of 0.3%) as other DPP-4 inhibitors available in Canada.
- **Exclusion of Other Relevant Comparators:** Other oral T2DM drugs in combination to metformin using maximum doses were considered only in sensitivity analyses and not in the base case. In addition, the manufacturer did not consider insulin as a comparator.

Issues for Consideration

The indication under review is a second-line treatment in combination with metformin. The manufacturer is requesting reimbursement as per the indications under review. The majority of public drug plans list DPP-4 inhibitor/metformin FDCs when insulin is not an option and after inadequate glycemic control on dual therapy of metformin and sulfonylurea. Unlike other DPP-4 inhibitors, alogliptin is not indicated as add-on to the dual therapy of metformin and sulfonylurea.

There is variation across drug plans in the list price of DPP-4 inhibitor/metformin FDCs. To assess the impact of these price variations, CDR performed a price reduction analysis (APPENDIX 1: PRICE REDUCTION ANALYSIS). The CDR analysis shows that the price of alogliptin/metformin FDC would need to be reduced by 6.6% from $2.74 per day to equal that of linagliptin/metformin FDC at $2.56 per day, the lowest-priced DPP-4 inhibitor/metformin FDC covered in Canada.

Alogliptin/metformin FDC is estimated to provide additional savings through dispensing fees and on the metformin component when dosing of metformin exceeds 1,000 mg per day. Compared with the individual drugs metformin (1,000 mg, 1,700 mg, and 2,000 mg daily) and alogliptin (25 mg daily), including markup and dispensing fee, alogliptin/metformin FDC results in cost savings ranging from $33 to $150 per patient, per year, depending on the metformin dose and number of days per claim. (See Table 6 in APPENDIX 3: REVIEWER WORKSHEETS.)

Results and Conclusions

At the submitted price of $1.37 per tablet ($2.74 daily), alogliptin/metformin is less costly than sitagliptin/metformin ($3.20 daily), is similarly priced to saxagliptin/metformin ($2.74 daily), but is more costly than linagliptin/metformin ($2.67 daily). Alogliptin/metformin FDC is less expensive than the individual components of alogliptin and metformin (same price for daily doses of 1,000 mg of metformin, but savings of $0.05 to $0.12 daily for doses > 1,000 mg daily, and one less dispensing fee per refill).

Alogliptin/metformin as a second-line drug would become a more costly option compared with other second-line treatments in non-fixed-dose combinations with metformin such as a sulfonylurea and pioglitazone; potentially leading to significant cost increases to public drug plans.

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.

Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 1: COST COMPARISON TABLE FOR DPP-4 INHIBITOR PLUS METFORMIN FIXED-DOSE COMBINATIONS AND INDIVIDUAL COMPONENTS, AND OTHER NON-INSULIN SECOND-LINE ANTIDIABETIC DRUGS USED IN COMBINATION WITH METFORMIN

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Alogliptin/metformin (Kazano)	**12.5/500 mg 12.5/850 mg 12.5/1000 mg**	**Tab**	**1.3700[a]**	**Two tablets daily**	**2.74**	**1,000**
Individual components						
Metformin	500 mg 850 mg	Tab	0.0587 0.0847[b]	500 mg three to four times daily	0.18–0.23	64–86
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	Tab	2.6177[a]	25 mg daily	2.62	955
Other dipeptidyl peptidase-4 (DPP-4) inhibitors plus metformin fixed-dose combinations						
Linagliptin/metformin (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	Tab	1.3337	Two tablets daily	2.67	974
Saxagliptin/ metformin (Komboglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	Tab	1.3716[b]	Two tablets daily	2.74	1,000
Sitagliptin/metformin (Janumet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg	Tab	1.6015	Two tablets daily	3.20	1,169
DPP-4 inhibitors						
Linagliptin (Trajenta)	5 mg	Tab	2.5500	5 mg daily	2.55	931
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	Tab	2.3690 2.8387	5 mg daily	2.84	1,036
Sitagliptin (Januvia)	100 mg	Tab	2.9527	100 mg daily	2.95	1,078
Insulin secretagogues, sulfonylureas						
Gliclazide (generics)	80 mg	Tab	0.0931	80 to 320 mg daily (in divided doses if > 160 mg daily)	0.09–0.37	34–136

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Gliclazide long acting (Diamicron MR)	30 mg 60 mg	ER tab	0.1405 0.2529	30 mg to 120 mg Daily	0.14–0.51	51–185
Glimepiride (generics)	1 mg 2 mg 4 mg	Tab	0.4851[c]	1 mg to 4 mg daily	0.49	177
Glyburide (generics)	2.5 mg 5.0 mg	Tab	0.0321 0.0574	2.5 mg to 20 mg daily (in divided doses if > 10 mg daily)	0.03–0.23	12–84
Subtype 2 sodium-glucose transport protein (SGLT-2) inhibitors						
Canagliflozin (Invokana)	100 mg 300 mg	Tab	2.8403[d]	100 or 300 mg daily	2.84	1,037
Glucagon-like peptide-1 (GLP-1) receptor agonist						
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/ mL)	149.4100[d]	10 mcg twice daily	4.98	1,817
Liraglutide (Victoza)	2 × 3 mL 3 × 3 mL	Pre-filled pen inj (6 mg/mL)	175.1900[d] 262.7800[d]	1.2 mg to 1.8 mg daily	5.84–8.76	2,131–3,197
Thiazolidinediones (TZDs)						
Pioglitazone (generics)	15 mg 30 mg 45 mg	Tab	0.8133[e] 1.1394[e] 1.7132[e]	15 mg to 45 mg daily	0.81–1.71	267–625
Rosiglitazone (Avandia)	2 mg 4 mg 8 mg	Tab	1.3755[e] 2.1584[e] 3.0865[e]	4 to 8 mg daily	2.16–3.09	788–1,126
Rosiglitazone/ metformin (Avandamet)	1/500 mg 2/500 mg 4/500 mg 2/1,000 mg 4/1,000 mg	Tab	0.6421[e] 1.1611[e] 1.5943[e] 1.2682[e] 1.7337[e]	4/1,000 to 8/2,000 mg daily in divided doses	2.32–3.47	847–1,266

DPP-4 = dipeptidyl peptidase-4; ER = extended release; MR = modified release; tab = tablet.
[a] Manufacturer's submission price.
[b] BC Drug Formulary (October 2014).[6]
[c] Manitoba Drug Formulary (October 2014).[7]
[d] McKesson Canada wholesale price (October 2014), includes markup.[8]
[e] Saskatchewan Drug Formulary (October 2014).[9]
Source: Ontario Drug Benefit (October 2014) prices unless otherwise indicated.[5]

APPENDIX 1: PRICE REDUCTION ANALYSIS

There is variation in the list price of DPP-4 inhibitor/metformin FDCs across participating drug plans. CDR calculated the price reduction that would be required to produce a price of alogliptin/metformin FDC equivalent to the least expensive DPP-4/metformin FDC currently reimbursed by public plans in Canada (linagliptin/metformin; $1.2784 per tablet, $2.56 per day, obtained from the British Columbia drug benefit plan in October 2014). As shown in Table 2, the price of alogliptin/metformin would need to be reduced by 6.6% to equal that of linagliptin/metformin at $2.56 per day, the lowest-priced DPP-4/metformin FDC covered in Canada. This would result in cost savings of up to $66 per patient per year had alogliptin/metformin been reimbursed at the requested price of $2.74 per day.

TABLE 2: CADTH COMMON DRUG REVIEW ANALYSIS ON PRICE FOR ALOGLIPTIN/METFORMIN

Current Daily Cost[a]	Scenario	Reduced Daily Cost[b]	Reduction (%)	Annual Savings
$2.74	Price reduction needed to equal the daily price of the least expensive DPP-4/metformin fixed-dose combination (linagliptin/metformin)	$2.56[c]	6.6%	$66[d]

DPP-4 = dipeptidyl peptidase-4.
[a] Manufacturer-submitted price.
[b] Dose not include markup or dispensing fees.
[c] Price from British Columbia drug formulary, October 2014.[6]
[d] Savings per patient per year.

APPENDIX 2: COSTS OF ADDITIONAL COMPARATORS

TABLE 3: COST COMPARISON OF INSULIN DRUGS

Drug/Comparator	Strength	Dosage Form	Price ($)	Cost per mL ($)
Short-acting insulin (human and analogues)				
Insulin aspart (NovoRapid)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	58.81 61.21 29.00	3.92 4.08 2.90
Insulin glulisine (Apidra)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	49.55 50.10 25.05	3.30 3.34 2.51
Insulin lispro (Humalog)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	55.27 55.27 27.61	3.68 3.68 2.76
Humulin R	100 U/mL	5 × 3 mL cartridge 10 mL vial	44.24 22.54	2.95 2.25
Novolin ge Toronto	100 U/mL	5 × 3 mL cartridge 10 mL vial	41.24 21.01	2.75 2.10
Intermediate-acting human insulin				
Humulin N	100 U/mL	5 × 3 mL cartridge 10 mL vial	44.24 22.54	2.95 2.25
Novolin ge NPH	100 U/mL	5 × 3 mL cartridge 10 mL vial	42.23 21.49	2.82 2.15
Long-acting insulin analogues				
Insulin glargine (Lantus)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	92.20 92.20 61.06	6.15 6.15 6.11
Insulin detemir (Levemir)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	101.68 106.76	6.78 7.12
Pre-mixed				
Biphasic insulin aspart 30/70 (NovoMix 30)	100 U/mL	5 × 3 mL cartridge	55.37	3.69
Lispro/lispro protamine 25/75 (Humalog Mix 25)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	55.92 55.09	3.73 3.67
Lispro/lispro protamine 50/50 (Humalog Mix 50)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	54.99 54.99	3.67 3.67
Humulin 30/70	100 U/mL	5 × 3 mL cartridge 10 mL vial	44.24 22.54	2.95 2.25
Novolin ge 30/70	100 U/mL	5 × 3 mL cartridge 10 mL vial	41.74 21.60	2.78 2.16
Novolin ge 40/60	100 U/mL	5 × 3 mL cartridge	42.04	2.80
Novolin ge 50/50	100 U/mL	5 × 3 mL cartridge	42.04	2.80

Source: Ontario Drug Benefit (October 2014) prices.[5]

APPENDIX 3: REVIEWER WORKSHEETS

SUMMARY OF MANUFACTURER'S SUBMISSION

TABLE 4: MANUFACTURER'S SUBMISSION

Drug Product	**Alogliptin/metformin (Kazano) 12.5/500 mg, 12.5/850 mg, 12.5/1,000 mg**
Treatment	Alogliptin/metformin 12.5 mg/500 mg, 12.5 mg/850 mg, 12.5 mg/1,000 mg twice daily
Comparator(s)	• Linagliptin/metformin 2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1,000 mg • Saxagliptin/metformin 2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1,000 mg • Sitagliptin metformin 50 mg/500 mg
Study Question	To conduct an economic evaluation of alogliptin plus metformin fixed-dose combination versus currently available DPP-4 inhibitor plus metformin fixed-dose combinations, in the treatment of T2DM
Type of Economic Evaluation	Cost-minimization analysis
Target Population	Patients with T2DM
Perspective	Canadian public payer
Outcome(s) Considered	• A1C change from baseline • Percentage of patients achieving target A1C < 7% • Weight • Hypoglycemic events
Key Data Sources	
Cost	Alberta Drug Benefit, Ontario Drug Benefit, and IMS Brogan
Clinical Efficacy	Manufacturer-conducted network meta-analysis
Harms	Manufacturer-conducted network meta-analysis
Time Horizon	One year
Results for Base Case	• Alogliptin/metformin fixed-dose combination was associated with additional cost of $26.50 and $73.00 when compared with linagliptin/metformin and saxagliptin/metformin fixed-dose combinations, respectively. • Alogliptin/metformin is expected to result in cost savings up to $122.28 when compared with sitagliptin/metformin fixed-dose combination.

A1C = glycated hemoglobin; T2DM = type 2 diabetes mellitus.

Manufacturer's Results

The manufacturer reported alogliptin/metformin to be more costly than two of the currently marketed DPP-4 inhibitor/metformin fixed-dose combination drugs. The unit cost of alogliptin/metformin was $1.37 compared with linagliptin/metformin, saxagliptin/metformin and sitagliptin/metformin with a unit cost of $1.33, $1.27, and $1.60 respectively (Table 5).

At the time this analysis was submitted to CDR for review, the linagliptin/metformin and saxagliptin/metformin FDCs were not yet listed in provincial formularies; prices were estimated using lowest wholesaler prices in the provinces.

TABLE 5: MANUFACTURER'S BASE-CASE ANALYSIS

Generic Name	Brand Name	Prince/Unit	Price/Year[a]	Costs (Savings)/ Year
Alogliptin/metformin (12.5/500 mg, 12.5/850 mg, 12.5/1,000 mg)	Kazano	$1.3700	$1,000.10	
Linagliptin/metformin (2.5/500 mg, 2.5/850 mg, 2.5/1,000 mg)	Jentadueto[b]	$1.3337[c]	$973.60	$26.50
Saxagliptin/metformin (2.5/500 mg, 2.5/850 mg, 2.5/1,000 mg)	Komboglyze[b]	$1.2700[d]	$927.10	$73.00
Sitagliptin/metformin (50/500 mg)	Janumet	$1.6015	$1,169.10	($169.00)

[a] Assuming 365 days/year, no drug plan parameters applied (markup, dispensing fee).
[b] This product was not yet listed in provincial formularies by the time this analysis was submitted for review by the CADTH Common Drug Review; lowest wholesaler price used.[5]
[c] Ontario Drug Benefit now lists linagliptin/metformin FDC at a flat price of $1.3337 per 2.5 mg/500 mg, 2.5 mg/850 mg, or 2.5 mg/1,000 mg tablet.[5]
[d] British Columbia drug benefit now lists saxagliptin/metformin FDC at a flat price of $1.3716 per 2.5 mg/500 mg, 2.5 mg/850 mg, or 2.5 mg/1,000 mg tablet.[6]
Source: Adapted from the manufacturer pharmacoeconomic submission, page 13, Table 5.[2]

Alogliptin/metformin FDC was less expensive than sitagliptin/metformin FDC. Based on lowest wholesaler price, the manufacturer estimates that alogliptin/metformin FDC will introduce cost (savings) to provincial drug plans, ranging from $26.50 annual cost versus linagliptin/metformin FDC up to $169 annual savings versus sitagliptin/metformin FDC. The manufacturer conducted sensitivity analyses comparing alogliptin/metformin FDC with other classes of oral T2DM drugs. Daily unit prices were compared assuming utilization over 365 days per year based on maximal dosage.

The manufacturer reported alogliptin/metformin FDC to be less expensive than any DPP-4 inhibitor free combination, saving $16.35 to $163.34 per year versus the free combinations. Also, alogliptin/metformin FDC was less expensive than rosiglitazone and metformin as a fixed- or free-dose combination, but more expensive than generic pioglitazone as a free-dose combination. Sulfonylurea + metformin free combinations were less expensive than alogliptin/metformin FDC. Finally, the manufacturer estimates alogliptin/metformin FDC to produce savings of a dispensing fee, compared to the free combination dose of alogliptin and metformin (Table 6). Alogliptin/metformin FDC offered additional savings on the metformin component, when metformin was dosed > 1,000 mg daily.

TABLE 6: MANUFACTURER'S RESULTS OF VARIOUS METFORMIN DOSES (INDIVIDUAL COMPONENTS)

Drug	Dosing	Metformin	Daily Cost	Cost per Year[a]
Alogliptin/metformin	**All strengths**		**$2.7400**	**$1,000.10**
Alogliptin	25 mg daily: $2.6177 × 1	500 mg b.i.d.: $0.0587 × 2	$2.7351	$998.31
		850 mg b.i.d.: $0.0847[b] × 2	$2.7871	$1,017.29
		1,000 mg b.i.d.: $0.0587 × 4	$2.8525	$1,041.16

b.i.d. = twice daily.
[a] Assuming 365 days/year, no drug plan parameters applied (markup, dispensing fee): Ontario Drug Benefit e-Formulary, November 2013.[5]
[b] Not funded in Ontario; Alberta drug plan.[10]
Source: Adapted from the manufacturer's pharmacoeconomic submission, page 13, Table 5.[2]

CDR Results

The manufacturer conducted a sensitivity analysis estimating the cost savings associated with alogliptin/metformin FDC compared with the free combination (Table 5). The manufacturer's analysis did not include drug plan parameters (i.e., markup and dispensing fee). CDR conducted a sensitivity analysis that takes the cost per day estimates as derived in Table 5 and incorporates markup and dispensing fees per Ontario Drug Benefit rules (i.e., 8% markup and $8.83 dispensing fee)[5] to estimate the annual cost per patient using 30 to 100 days per claim. Compared with the individual drugs metformin (1,000 mg, 1,700 mg, and 2,000 mg daily) and alogliptin (25 mg daily), including markup and dispensing fee, alogliptin/metformin FDC results in cost savings ranging from $33 to $150 per patient, per year, depending on the metformin dose and number of days per claim (Table 7).

TABLE 7: CADTH COMMON DRUG REVIEW ANNUAL COST COMPARISON (INCLUDING MARKUP AND DISPENSING FEE)

Drug/ Comparator	Strength	Daily Dose	Daily Drug Cost	Daily Drug Cost (With Markup)[a]	Dispensing Fee per Claim[a]	Cost per Claim	Annual Cost per Patient[b]	Annual Savings Compared With Individual Components ($)
Alogliptin + metformin (Kazano)	**12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg**	Two tablets daily	**$2.7400**	**$2.9592**	**$8.83**	**$97.61–$304.75**	**$1,171–$1,219**	**$33–$104 $56–$124 $84–$150**
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	25 mg daily	$2.6177	$2.8271	$8.83	$93.64–$291.54	$1,12 –$1,166	NA
Metformin (generics)	500 mg 850 mg 1,000 mg	1,000 to 2,000 mg daily	$0.1174 $0.1694 $0.2348	$0.1268 $0.1830 $0.2536	$8.83	$12.63–$21.51 $14.32–$27.13 $16.44–$34.19	$86–$152 $109–$172 $137–$197	NA
Total (alogliptin + metformin)			**$2.7351 $2.7871 $2.8525**	**$2.9539 $3.0101 $3.0807**	**$17.66**	**$106.28–$313.05 $107.96–$318.67 $110.08–$325.75**	**$1,252–$1,275 $1,275–$1,296 $1,303–$1,321**	

NA = not applicable.

[a] The markup and dispensing fee used in the table is based on Ontario Drug Benefit (ODB) rules, that is, an 8% markup and an $8.83 dispensing fee.[5]

[b] It was assumed that each claim would range from 30 to 100 days; thus, dispensing fees paid 3.65 (~ 4) to 12 times per year.

TABLE 8: KEY LIMITATIONS

Identified Limitation	Description	Implication
NMA limitations	The trials included in the NMA presented potential limitations such as heterogeneity between included RCTs in baseline characteristics and study durations. The primary outcome in most studies was change in A1C from baseline; thus, it remains unclear whether the outcomes for body weight and hyperglycemic events were adequately powered in the respective studies to detect meaningful differences.	There remains uncertainty over the treatment similarities as perceived from the manufacturer-submitted NMA
Appropriate comparators were omitted from the base-case analysis	The manufacturer's base case did not consider oral therapies in other drug classes that are less expensive than alogliptin and available as second-line treatment of T2DM: sulfonylureas, thiazolidinediones. The manufacturer conducted sensitivity analyses that compared the other oral T2DM drugs in combination with metformin using maximum doses. In addition, the manufacturer did not consider insulin as a comparator.	The cost savings of alogliptin may be overestimated with the exclusion of other comparators from the base-case analysis

A1C = glycated hemoglobin; NMA = network meta-analysis; RCT = randomized controlled trial; T2DM = type 2 diabetes mellitus.

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