Common Drug Review
Pharmacoeconomic Review Report

August 2015

Drug	alogliptin (Nesina)
Indications under review	1) in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycemic control 2) in combination with a sulfonylurea when diet and exercise plus a sulfonylurea alone do not provide adequate glycemic control
Listing request	As per indications under review
Manufacturer	Takeda Canada Inc.

Alogliptin (Nesina) Common Drug Review Pharmacoeconomic Report was prepared using PharmaStat data from IMS Health Canada Inc. The analyses, conclusions, opinions, and statements expressed are those of CADTH and not those of IMS Health Canada Inc.

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ABBREVIATIONS

A1C	glycated hemoglobin
CDR	CADTH Common Drug Review
DPP-4	dipeptidyl peptidase-4
NMA	network meta-analysis

SUMMARY

Background

Alogliptin (Nesina) is an oral antihyperglycemic drug belonging to the dipeptidyl peptidase-4 (DPP-4) inhibitor class. This CADTH Common Drug Review (CDR) focuses on the two following indications:

- in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycemic control
- in combination with a sulfonylurea when diet and exercise plus a sulfonylurea alone do not provide adequate glycemic control.

The recommended dose of alogliptin is 25 mg once daily for most patients and 6.25 mg to 12.5 mg once daily for patients with moderate to severe renal impairment. The manufacturer submitted a flat price of $2.6177 per 6.25 mg, 12.5 mg, or 25 mg tablet ($2.62 daily).

Upon submission, the manufacturer requested listing of alogliptin in a manner similar to other DPP-4 inhibitors currently available in Canada. Upon review of the draft CDR clinical and pharmacoeconomic reports, the manufacturer asked that the requested listing criteria be modified to reflect the two indications under review.

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost-minimization analysis[1] comparing alogliptin (6.25 mg, 12.5 mg, or 25 mg) with other DPP-4 inhibitors (linagliptin 5 mg, saxagliptin 5 mg, and sitagliptin 100 mg), in patients with type 2 diabetes mellitus over a one-year time frame. Because no head-to-head trials were available comparing alogliptin with saxagliptin, sitagliptin, or linagliptin, the assumption of similar efficacy and safety was based on manufacturer-funded network meta-analyses (NMAs) comparing effects of each drug in terms of change in glycated hemoglobin (A1C) from baseline, percentage of patients achieving target A1C of less than 7%, weight change, and hypoglycemic events.[2,3] The NMAs suggested that there are no differences among DPP-4 inhibitors either as monotherapy or combination therapy on A1C, body weight, and hypoglycemic events.[1] 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, and these were obtained from the Ontario Drug Benefit program (November 2013).[4] Because alogliptin, saxagliptin, linagliptin, and sitagliptin are from 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 and a weighted average DPP-4 inhibitor cost were derived based on the available 2013 Ontario claims data from IMS Brogan (first three quarters of 2013) (Table 5). Based on the utilization for that period, 77.5%, 11.3%, and 11.2% of claims for DPP-4 inhibitors were from sitagliptin, saxagliptin, and linagliptin, respectively. Using more recent data (up to June 2014) and Ontario as a reference, CDR found that 69%, 11.6%, and 17.6% of claims for DPP-4 inhibitors were from sitagliptin, saxagliptin, and linagliptin, respectively.

Key Limitations

- **Limitations of the NMAs:** There was heterogeneity among randomized controlled trials included in the NMAs 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 change and hypoglycemic events were adequately powered in the respective studies to detect meaningful differences. A limitation of the Craddy et al.[2] NMA was the pooling of studies of various sulfonylureas, a likely source of heterogeneity. A further key limitation of the Craddy et al.[2] NMA was the conclusion of similar numerical efficacy among DPP-4 inhibitors, based on the overlap in the 95% credible intervals for the treatment effects. This assumption is not statistically valid in a Bayesian framework. However, the subsequent NMA by Tolley et al.[3] suggested that there are no differences among DPP-4 inhibitors in terms of change in A1C, change in body weight, and hypoglycemic events, and 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.
- **Exclusion of other relevant comparators:** The manufacturer did not consider oral therapies in other drug classes (sulfonylureas and thiazolidinediones) that are less expensive than alogliptin and available as second-line treatment of type 2 diabetes. In addition, the manufacturer did not consider insulin as a comparator.

Issues for Consideration

- The indications under review are second-line treatment in combination with metformin or a sulfonylurea. The manufacturer is requesting reimbursement for the indications under review. However, the majority of public drug plans list DPP-4 inhibitors after trial or intolerance/contraindication to both metformin and a sulfonylurea.
- Alogliptin is indicated in Canada as third-line drug, with pioglitazone plus metformin or insulin plus metformin. However, unlike other DPP-4 inhibitors available in Canada, alogliptin is not indicated for use in combination with metformin and a sulfonylurea. According to clinical expert opinion, there is potential for off-label use of alogliptin as a third-line treatment with metformin plus a sulfonylurea.
- There is variation across drug plans in the list price of DPP-4 inhibitors. In addition, previous Canadian Drug Expert Committee recommendations indicated that drug plan costs for saxagliptin should not exceed the cost of other DPP-4 inhibitors.[5] To assess the impact of these price variations, CDR performed a price-reduction analysis (see Appendix 1: PRICE-REDUCTION ANALYSIS). The CDR analysis shows that the price of alogliptin would need to be reduced by 14% from $2.62 per day to equal that of linagliptin at $2.25 per day, the lowest priced DPP-4 inhibitor covered in Canada.

Results and Conclusions

At the submitted daily cost of $2.62, alogliptin is less costly than sitagliptin 100 mg ($2.95 daily), the most frequently used DPP-4 inhibitor in Canada, and saxagliptin 5 mg ($2.84 daily), but more costly than linagliptin 5 mg ($2.25 to $2.55). Based on Ontario 2014 claims data, alogliptin is less expensive than the average weighted daily cost of DPP-4 inhibitors ($2.86).

Alogliptin as a second-line drug would be a more costly option than other second-line treatments for type 2 diabetes such as metformin, a sulfonylurea, pioglitazone, or insulin, 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. Cost of insulin drugs is also presented in Appendix 2: COSTS OF ADDITIONAL COMPARATORS.

Existing product listing agreements are not reflected in the table; therefore, costs may not represent the actual costs to public drug plans.

TABLE 1: COST COMPARISON TABLE FOR DPP-4 INHIBITORS AND OTHER SECOND-LINE ORAL DRUGS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	tab	2.6177[a]	25 mg daily	2.62	955
Dipeptidyl peptidase-4 (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
Biguanides						
Metformin	500 mg 850 mg	tab	0.0587 0.1186[b]	500 mg three to four times daily	0.18 to 0.23	64 to 86
Insulin secretagogues, sulfonylureas						
Gliclazide (generics)	80 mg	tab	0.0931	80 mg to 320 mg daily (in divided doses if > 160 mg daily)	0.09 to 0.37	34 to 136
Gliclazide long-acting (Diamicron MR)	30 mg 60 mg	ER tab	0.1405 0.2529	30 mg to 120 mg daily	0.14 to 0.51	51 to 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 to 0.23	12 to 84
Thiazolidinediones						
Pioglitazone (generics)	15 mg 30 mg 45 mg	tab	0.8133[b] 1.1394[b] 1.7132[b]	15 mg to 45 mg daily	0.81 to 1.71	267 to 625

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Rosiglitazone (Avandia)	2 mg 4 mg 8 mg	tab	1.3755[b] 2.1584[b] 3.0865[b]	4 mg to 8 mg daily	2.16 to 3.09	788 to 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[b] 1.1611[b] 1.5943[b] 1.2682[b] 1.7337[b]	4/1,000 mg to 8/2,000 mg daily in divided doses	2.32 to 3.47	847 to 1,266
Sodium-glucose cotransporter-2 inhibitors						
Canagliflozin (Invokana)	100 mg 300 mg	tab	2.8403[d]	100 mg or 300 mg daily	2.84	1,037
Glucagon-like peptide-1 receptor agonists						
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 (6 mg/mL)	175.1900[d] 262.7800[d]	1.2 mg to 1.8 mg daily	5.84 to 8.76	2,131 to 3,197

ER = extended release; tab = tablet.
[a] Manufacturer's submission price.[1]
[b] Saskatchewan Drug Formulary (August 2014).[6]
[c] Manitoba Drug Formulary (August 2014).[8]
[d] McKesson Canada wholesale price (August 2014).[7]
Source: Ontario Drug Benefit program (October 2014) prices unless otherwise indicated.[4]

APPENDIX 1: PRICE-REDUCTION ANALYSIS

Due to variation in reimbursement prices across Canada, the CADTH Common Drug Review (CDR) calculated the price reduction that would be required to produce a price of alogliptin equivalent to the least expensive dipeptidyl peptidase-4 inhibitor currently reimbursed by public plans in Canada (linagliptin, $2.25 per day). The price for linagliptin was obtained from the Nova Scotia drug benefit plan, which was chosen because it is the lowest publicly available price. There is variation in linagliptin reimbursement prices across Canada. As shown in Table 2 below, the price of alogliptin would need to be reduced by 14% from $2.62 per day to equal that of linagliptin at $2.25 per day. The price reduction would result in cost savings of up to $135 per patient per year for alogliptin versus the submitted price of $2.62 per day.

TABLE 2: CADTH COMMON DRUG REVIEW ANALYSIS OF PRICE FOR ALOGLIPTIN

Current Price[a]	Scenario	Reduced Price[b]	% Price Reduction	Annual Savings
$2.62	Price reduction needed to equal the price of the least expensive DPP-4 (linagliptin)	$2.25	14%	$135[c]

DPP-4 = dipeptidyl peptidase-4.
[a] Manufacturer-submitted price.[1]
[b] Dose does not include markup or dispensing fees.
[c] Savings per patient per year.

APPENDIX 2: COSTS OF ADDITIONAL COMPARATORS

TABLE 3: COST COMPARISON OF INSULIN DRUGS

Drug/Comparator	Strength (U/mL)	Dosage Form	Price ($)	Cost per mL ($)
Short-acting insulin (human and analogues)				
Insulin aspart (NovoRapid)	100	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	5 × 3 mL cartridge 5 × 3 disposable pen 10 mL vial	49.55 50.10 25.05	3.30 3.34 2.51
Insulin lispro (Humalog)	100	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	5 × 3 mL cartridge 10 mL vial	44.24 22.54	2.95 2.25
Novolin ge Toronto	100	5 × 3 mL cartridge 10 mL vial	41.24 21.01	2.75 2.10
Intermediate-acting human insulin				
Humulin N	100	5 × 3 mL cartridge 10 mL vial	44.24 22.54	2.95 2.25
Novolin ge NPH	100	5 × 3 mL cartridge 10 mL vial	42.23 21.49	2.82 2.15
Long-acting insulin analogues				
Insulin glargine (Lantus)	100	5 × 3 mL cartridge 5 × 3 disposable pen 10 mL vial	92.20 92.20 61.06	6.15 6.15 6.11
Insulin detemir (Levemir)	100	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	5 × 3 mL cartridge	55.37	3.69
Lispro/lispro protamine 25/75 (Humalog Mix 25)	100	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	5 × 3 mL cartridge 5 × 3 mL disposable pen	54.99 54.99	3.67 3.67
Humulin 30/70	100	5 × 3 mL cartridge 10 mL vial	44.24 22.54	2.95 2.25
Novolin ge 30/70	100	5 × 3 mL cartridge 10 mL vial	41.74 21.60	2.78 2.16
Novolin ge 40/60	100	5 × 3 mL cartridge	42.04	2.80
Novolin ge 50/50	100	5 × 3 mL cartridge	42.04	2.80

NPH = neutral protamine Hagedorn.
Source: Ontario Drug Benefit program (October 2014) prices.[4]

APPENDIX 3: REVIEWER WORKSHEETS

TABLE 4: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug product	**Alogliptin (Nesina) 6.25 mg, 12.5 mg, 25 mg**
Treatment	Alogliptin 25 mg once daily
Comparators	Linagliptin 5 mg, saxagliptin 5 mg, sitagliptin 100 mg daily
Study question	To conduct an economic evaluation of alogliptin versus currently available DPP-4 inhibitor drugs, as a second-line treatment of type 2 diabetes mellitus
Type of Economic Evaluation	Cost-minimization analysis
Target Population	Patients with type 2 diabetes
Perspective	Canadian public payer
Outcomes Considered	Change in A1C from baseline Percentage of patients achieving target A1C < 7% Weight change Hypoglycemic events
Key Data Sources	
Cost	Ontario Drug Benefit program, Quebec drug plan
Clinical Efficacy	Manufacturer-conducted network meta-analysis
Harms	Manufacturer-conducted network meta-analysis
Time Frame	One year
Results for Base Case	Alogliptin was associated with incremental cost of $24.71 when compared with linagliptin as second-line treatment. Alogliptin is expected to result in cost savings up to $122.28 when compared with sitagliptin and saxagliptin as second-line treatment.

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4.

2. Manufacturer's Results

The manufacturer reported alogliptin to be less costly than the two most commonly used currently marketed dipeptidyl peptidase-4 (DPP-4) inhibitors. The daily cost of alogliptin was $2.62 compared with linagliptin, saxagliptin, and sitagliptin, with a daily cost of $2.55, $2.84 (for the more common 5 mg dose), and $2.95, respectively (Table 5).

TABLE 5: MANUFACTURER'S COST-MINIMIZATION ANALYSIS

Generic Name	Brand Name	Price/Unit	Price/Year[a]	Costs (Savings)/ Year
Alogliptin (6.25 mg, 12.5 mg, 25 mg)	Nesina	$2.6177	$955.46	
Linagliptin (5 mg)	Trajenta	$2.5500	$930.75	$24.71
Saxagliptin (5 mg)	Onglyza	$2.8387 (5 mg)[b]	$1,036.13	($80.66)
Sitagliptin (25 mg, 50 mg, 100 mg)	Januvia	$2.9527	$1,077.74	($122.28)
Ontario weighted market average[c] (first three quarters of 2013)		$2.8947	$1,056.57	($101.11)

Source: Manufacturer pharmacoeconomic submission, page 13, Table 5.[1]
[a] Assuming 365 days/year, no drug plan parameters applied (markup, dispensing fee).
[b] The default daily dose is 5 mg. A 2.5 mg tablet ($2.3690) is also available for special populations (renal impairment).
[c] Composed of 77.5% sitagliptin claims, 11.3% saxagliptin claims, and 11.2% linagliptin claims.

Alogliptin was less expensive than sitagliptin and saxagliptin. The manufacturer estimates that the cost impact of alogliptin will range from $24.71 annual incremental cost versus linagliptin up to $122.28 annual savings versus sitagliptin. The manufacturer also reported that alogliptin was 10% less expensive than Ontario's weighted market average cost (composed of 77.5% sitagliptin claims, 11.3% saxagliptin claims, and 11.2% linagliptin claims). Compared with the average cost of current DPP-4 inhibitors, the manufacturer expects alogliptin to introduce savings of $101.11 per patient per year.

The manufacturer conducted sensitivity analyses comparing alogliptin with other classes of oral type 2 diabetes drugs. Metformin was excluded because it was considered platform therapy for all patients. Daily unit prices were compared, as well as the 30-day claim cost based on maximum dosage. The results of the sensitivity analyses show alogliptin to be more expensive than linagliptin but less expensive than saxagliptin and sitagliptin. Results also show DPP-4 inhibitors to be more expensive than sulfonylureas and generic thiazolidinediones.

3. CADTH Common Drug Review Results

The submitted price for alogliptin ($2.62 per day) is already lower than that of sitagliptin ($2.95 per day), another DPP-4 inhibitor approved in Canada that is considered to be the most widely used drug of this class among drug plans in Canada, with an approximate market share of 69% in Ontario as of June 2014.[4]

The manufacturer had submitted a weighted market average cost ($2.89) based on claims data from the first three quarters of 2013 in Ontario. The CADTH Common Drug Review (CDR) calculated the utilization of DPP-4 inhibitors in Ontario using claims data from the first two quarters of 2014 and estimated an updated weighted market average price for alogliptin. Price data were obtained from the Ontario Drug Benefit program. The results in Table 6 indicate that the price of alogliptin is lower than that of saxagliptin (5 mg) and sitagliptin as well as lower than the updated Ontario weighted market average price.

TABLE 6: CADTH COMMON DRUG REVIEW ANALYSIS OF PRICE FOR ALOGLIPTIN USING WEIGHTED AVERAGE COST OF DPP-4 INHIBITORS

Generic Name	Price/Unit	% Claims
Alogliptin (6.25 mg, 12.5 mg, 25 mg)	$2.6177	
Linagliptin (5 mg)	$2.5500	17.6%
Saxagliptin (5 mg)	$2.8387 (5 mg)[a]	11.6%
Sitagliptin (25 mg, 50 mg, 100 mg)	$2.9527	69.0%
Ontario weighted market average[b] (first two quarters of 2014)	$2.8584	

DPP-4 = dipeptidyl peptidase-4.
[a] The market share for saxagliptin 2.5 mg (available for renal impairment) is approximately 1.7%.
[b] Ontario weighted average cost was calculated based on the available 2014 claims data from IMS Health (first two quarters of 2014).[9]

TABLE 7: KEY LIMITATIONS

Identified Limitation	Description	Implication
Limitations of NMAs	The trials included in the NMAs presented potential limitations such as heterogeneity between included randomized controlled trials 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 change and hypoglycemic events were adequately powered in the respective studies to detect meaningful differences.	There remains some uncertainty over the treatment similarities as perceived from the manufacturer-submitted NMAs.
Appropriate comparators were omitted	The manufacturer acknowledged the exclusion of SUs and thiazolidinediones based on their associated risks of hypoglycemia and cardiovascular risks, respectively. According to a CADTH report on optimal use of antidiabetic drugs in diabetes, SUs were considered the most cost-effective treatments for second-line therapy. Also, for the base case, the manufacturer did not consider oral therapies in other drug classes that are less expensive than alogliptin and available for treatment of type 2 diabetes.	The cost savings of alogliptin may be overestimated owing to the exclusion of other comparators from the base-case analysis.

A1C = glycated hemoglobin; NMA = network meta-analysis; SU = sulfonylurea.

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