Common Drug Review
Pharmacoeconomic Review Report

October 2015

Drug	Empagliflozin (Jardiance)
Indication	For adults with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea when diet, exercise, and dual therapy (with metformin plus a sulfonylurea) do not provide adequate glycemic control
Listing request	List in a similar manner to other SGLT-2 inhibitors and/or DPP-4 inhibitors
Dosage form(s)	10 mg and 25 mg tablet
NOC date	July 23, 2015
Manufacturer	Boehringer Ingelheim

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

TABLE OF CONTENTS

Tables

ABBREVIATIONS

AIC	glycated hemoglobin
CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
DPP-4	dipeptidyl peptidase-4
NMA	network meta-analysis
ODB	Ontario Drug Benefit
SGLT-2	sodium glucose cotransporter-2

SUMMARY

Background

Empagliflozin (Jardiance) is a once-daily oral antidiabetic drug belonging to the sodium glucose cotransporter-2 (SGLT-2) inhibitor class. It promotes urinary glucose excretion. This review by the CADTH Common Drug Review (CDR) will focus on the following indication:

- For adults with type 2 diabetes mellitus, to improve glycemic control in combination with metformin and a sulfonylurea when diet, exercise, and dual therapy (with metformin plus sulfonylurea) do not provide adequate glycemic control.

The recommended dose of empagliflozin is 10 mg once daily. This dose can be increased to 25 mg once daily in patients who tolerate empagliflozin but need additional glycemic control.[1] The manufacturer submitted a price of $2.6177 per 10 mg or 25 mg tablet ($2.62 daily).

The manufacturer is requesting a listing in a manner similar to other SGLT-2 inhibitors and/or dipeptidyl peptidase (DPP)-4 inhibitors.[2]

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost comparison[3] of empagliflozin (10 mg and 25 mg) and other SGLT-2 inhibitors (canagliflozin and dapagliflozin — not approved in Canada for third-line therapy at the time of the CDR review) and DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin), in patients with type 2 diabetes over a one-year time frame. Because no head-to-head trials were available for empagliflozin and the selected comparators, the assumption of similar efficacy and safety was based on a manufacturer-funded network meta-analysis (NMA) comparing the effects of each drug added on to metformin and a sulfonylurea in terms of glycated hemoglobin (A1C) change from baseline, weight, systolic blood pressure, and hypoglycemic events.[4] Based on the NMA, the manufacturer suggested that empagliflozin (10 mg and 25 mg) is associated with similar changes in A1C and risk of hypoglycemic events compared with other SGLT-2 inhibitors and with DPP-4 inhibitors. Both doses of empagliflozin showed a statistically significant better response for body weight compared with DPP-4 inhibitors.[3]

The cost analysis was conducted from the Canadian public payer perspective. Only drug acquisition costs were considered, which were obtained from the Ontario Drug Benefit (ODB) Program in April 2015.[5] ODB markup and dispensing fees were also incorporated to estimate the average annual cost per patient. The manufacturer assumed that all other aspects of patient management, such as routine patient care and adverse events, were equivalent for all comparators. For the base-case analysis, the unit prices of SGLT-2 inhibitors were obtained from IMS Brogan DeltaPA, and a weighted average SGLT-2 inhibitor class cost was estimated by assuming an equal market share. For DPP-4 inhibitors, the unit drug prices and a weighted average class cost were derived based on the available 2014 ODB claims data from IMS Brogan (Q1 to Q4, 2014) (see Table 6).

Key Limitations

- **Limitations with the network meta-analyses:** As stated in the CDR clinical report (Appendix 6), most of the comparisons in the network of evidence were informed by a single trial. The heterogeneity of the estimates for hypoglycemic events was high. For urogenital infections, no NMA could be conducted because only one trial reported this adverse event. Furthermore, many comparators that were deemed relevant in the CDR review protocol were not included in the manufacturer's literature search, or the results were not presented (e.g., insulin).

- **Exclusion of other relevant comparators:** The manufacturer did not consider insulin as a comparator, despite including insulin studies in the NMA. In addition, the manufacturer did not consider oral therapies in other drug classes that are less expensive than empagliflozin and used as third-line treatment of type 2 diabetes, such as alpha-glucosidase inhibitors (acarbose) and pioglitazone, although the latter is not frequently used because of safety issues.
- **Inappropriate comparator dosage strengths included:** The manufacturer submitted a weighted average cost of the DDP-4 inhibitors based on public claims data from the Q1 to the Q4 period in 2014 in Ontario. It is important to note that all dosage strengths were included in the manufacturer's calculations. This may be inappropriate, as lower strengths of sitagliptin (25 mg, 50 mg) and saxagliptin (2.5 mg) are typically used in patients with renal insufficiency, whereas the product monograph for empagliflozin[1] specifies that empagliflozin is not recommended for use in such patients with estimated glomerular filtration rate < 45 mL/min/1.73 m^2.[1] Thus, empagliflozin is unlikely to replace these lower-dose DPP-4 inhibitors. Including those doses may increase the weighted average cost, depending on their relative prices and/or market shares.
- **Interpretation of results:** The savings reported by the manufacturer arising from the price differential between empagliflozin and the weighted class average price will be realized only if empagliflozin replaces existing comparators in the proportion assumed by the manufacturer, based on current market shares. This is highly unlikely, given the fact that existing comparators, especially leading ones, have a market advantage over a new entrant. It is thus more appropriate to compare the price of empagliflozin with each comparator individually.
- **Updated comparator prices available:** Since the manufacturer conducted its economic analysis, alogliptin has been listed on the Quebec Formulary at $2.10 per day, substantially lower than the cost estimated by the manufacturer, which could be the case for other public formularies in the near future.

Issues for Consideration

Empagliflozin is the third SGLT-2 inhibitor approved in Canada, following canagliflozin and dapagliflozin, and the second SGLT-2 indicated for use as add-on therapy to metformin and a sulfonylurea (dapagliflozin was not approved as third-line therapy at the time of the review).

- Based on the Canadian Drug Expert Committee (CDEC) recommendation for canagliflozin, in which the condition for listing was that "when added on to metformin and a sulfonylurea, [canagliflozin] should not exceed the drug plan cost of DPP-4 inhibitors,"[6] the price of empagliflozin would need to be reduced by 14% from $2.62 per day to equal that of linagliptin ($2.25 per day) in Nova Scotia, the lowest-priced DPP-4 inhibitor covered by CDR-participating drug plans (see Appendix 1).
- If empagliflozin is added to the existing drugs, there are two possible effects: an expansion of the market for the SGLT-2 class, and substitution within the DPP-4 and SGLT-2 inhibitor classes. If the availability of empagliflozin expands the overall use of the SGLT-2 therapeutic class of drugs at the expense of less costly comparators, a further price reduction should be considered.

Results and Conclusions

At the submitted price of $2.62 per patient daily, the cost of empagliflozin is the same as canagliflozin. Compared with the list prices of DPP-4 inhibitors, empagliflozin is less costly than sitagliptin ($2.98 daily) and the 5 mg dose of saxagliptin ($2.88 daily), but is more costly than linagliptin ($2.25 to $2.55 daily) and alogliptin ($2.10 daily, based on Quebec Formulary price). Empagliflozin is more costly than pioglitazone, acarbose, and insulin.

Based on list prices, the daily cost of empagliflozin would need to be reduced by 14% to equal that of linagliptin ($2.25, based on Nova Scotia Formulary), the least costly DPP-4 inhibitor listed on a CDR-

participating drug plan. If the availability of empagliflozin expands the overall use of this therapeutic class of drugs and results in substitution of less costly comparators, a further price reduction should be considered.

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, thus, the table may not represent the actual costs to public drug plans.

The cost of insulin agents is also presented in Appendix 2.

TABLE 1: COST COMPARISON TABLE FOR NON-INSULIN AGENTS USED IN COMBINATION WITH METFORMIN AND A SULFONYLUREA

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Empagliflozin (Jardiance)	10 mg 25 mg	Tab	2.6177[a]	10 or 25 mg daily	2.62	955
Sodium glucose cotransporter (SGLT-2) inhibitors						
Canagliflozin (Invokana)	100 mg 300 mg	Tab	2.6177	100 or 300 mg daily	2.62	955
Dapagliflozin[b] (Forxiga)	5 mg 10 mg	Tab	NA	5 or 10 mg daily	NA	NA
Dipeptidyl peptidase-4 (DPP-4) inhibitors						
Sitagliptin (Januvia)	25 mg 50 mg 100 mg	Tab	2.9790	100 mg daily	2.98	1,087
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	Tab	2.3997 2.8753	5 mg daily	2.88	1,049
Linagliptin (Trajenta)	5 mg	Tab	2.5500[c]	5 mg daily	2.55	931
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	Tab	2.1000[d]	25 mg daily	2.10	767
Glucagon-like peptide-1 (GLP-1) receptor agonist						
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/mL)	NA	10 mcg twice daily	NA	NA
Liraglutide (Victoza)	6 mg/mL	Pre-filled pen (3 x 3 mL)	205.47[e]	1.2 mg to 1.8 mg daily	4.57 to 6.85	1,667 to 2,500
Thiazolidinediones (TZDs)						

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Pioglitazone (generics)	15 mg 30 mg 45 mg	Tab	0.3800[e] 0.5360[e] 0.8075[e]	15 mg to 45 mg daily	0.38 to 0.81	139 to 295
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 to 3.09	788 to 1,126
Rosiglitazone / metformin (Avandamet)	2/500 mg 4/500 mg 2/1000 mg 4/1000 mg	Tab	1.1611[e] 1.5946[e] 1.2682[e] 1.7337[e]	4/1,000 to 8/2,000 mg daily in divided doses	2.32 to 3.47	847 to 1,266
Alpha-glucosidase inhibitors						
Acarbose (Glucobay)	50 mg 100 mg	Tab	0.2695 0.3732	50 to 100 mg 3 times daily	0.81 to 1.12	295 to 409

CDR = CADTH Common Drug Review; NA = not applicable.
[a] Manufacturer's submission price.
[b] Dapagliflozin was not approved for third-line therapy (added on to metformin and a sulfonylurea) at the time of the CDR review.
[c] There is variability in the pricing of linagliptin among CDR-participating drug plans. The lowest price identified by CDR was on the Nova Scotia Formulary (2.2500 per tab, August 2015).
[d] Quebec Drug Formulary (Aug 2015).
[e] Saskatchewan Drug Formulary (Aug 2015).
Source: Ontario Drug Benefit (Aug 2015) prices unless otherwise indicated.

APPENDIX 1: PRICE REDUCTION ANALYSIS

In order to assess the class effect and the impact of differences in pricing across jurisdictions, two price-reduction scenarios were analyzed by the CADTH Common Drug Review (CDR), considering:

- Empagliflozin as a third-line treatment of type 2 diabetes with the sodium glucose cotransporter (SGLT)-2 inhibitors and dipeptidyl peptidase (DDP)-4 inhibitors as key comparators.

First Scenario

CDR calculated the price reduction that would be required for empagliflozin to be equivalent to the least expensive SGLT-2 or DPP-4 inhibitor currently reimbursed by CDR-participating drug plans as an add-on therapy to metformin and a sulfonylurea (linagliptin; $2.25 per day). The price for linagliptin was obtained from the Nova Scotia drug benefit plan, as the lowest publicly available price, noting variation in linagliptin prices across CDR-participating drug plans. As shown in Table 3, the price of empagliflozin would need to be reduced by 14% from $2.62 per day to equal that of linagliptin at $2.25 per day, which would result in cost savings of up to $134.21 per patient per year compared with the manufacturer's submitted price.

Second Scenario (Exploratory)

If it is assumed that the pricing of the SGLT-2 inhibitor class may follow that of the DPP-4 inhibitors, the pricing of the DPP-4 inhibitors in sequence would be a good reference for the SGLT-2 inhibitor class. Using a price ratio equal to that of the second or third drug to the first-listed DDP-4 inhibitor, CDR calculated the price reduction that would be required for empagliflozin as compared with canagliflozin (based on the Quebec Formulary price). The price ratio of the third-to-the-first DPP-4 inhibitor is almost identical, at 85.6%, using either the Ontario or Quebec list prices (Table 2). As shown in Table 3 below, using the Ontario third-to-first price ratio, the price of empagliflozin would need to be reduced by 14.4%, which would result in cost savings of up to $137.59 per patient per year had empagliflozin been reimbursed at the submitted price of $2.62 per day.

TABLE 2: PRICE RATIO FOR DPP-4 INHIBITORS

Drug/Comparator	Strength	Dosage Form	Quebec List Price ($)	Ontario List Price ($)
Dipeptidyl peptidase-4 (DPP-4) inhibitors				
Sitagliptin (Januvia)	25 mg 50 mg 100 mg	Tab	2.6177	2.9790
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	Tab	2.300	2.3997 2.8753
Linagliptin (Trajenta)	5 mg	Tab	2.2500	2.5500
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	Tab	2.1000	NA
Price ratio Saxagliptin 5 mg:Sitagliptin			87.9%	96.5%
Price ratio Linagliptin:Sitagliptin			86.0%	85.6%

DPP-4 = dipeptidyl peptidase-4; NA = not applicable.

TABLE 3: CADTH COMMON DRUG REVIEW PRICE REDUCTION SCENARIOS FOR EMPAGLIFLOZIN

Current Price[a]	Scenario	Reduced Price[b]	% Price Reduction	Annual Savings[c]
$2.62	Price reduction needed to equal the price of the least expensive SGLT-2 and DPP-4 (linagliptin)	$2.25	14.0%	$134.21
$2.62	Price reduction needed to equal 85.6% of the price of the first-listed SGLT-2 inhibitor (canagliflozin)	$2.24	14.4%	$137.59
$2.62	Price reduction needed to equal 96.5% of the price of the first-listed SGLT-2 inhibitor (canagliflozin)	$2.53	3.5%	$33.26

DPP-4 = dipeptidyl peptidase-4; SGLT-2 = sodium glucose cotransporter.
[a] Manufacturer-submitted price.[7]
[b] Daily cost does not include markup or dispensing fees.
[c] Savings per patient per year.

In addition to therapeutic competition between agents in the two classes of drugs, market size is also an important factor to consider when negotiating prices. If the availability of empagliflozin expands the overall use of this therapeutic class of drugs and results in substitution of less costly comparators, a further price reduction should be considered.

APPENDIX 2: COSTS OF ADDITIONAL COMPARATORS

TABLE 4: COST COMPARISON TABLE FOR INSULIN AGENTS

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 disposable pen 10 mL vial	50.00 50.35 22.06	3.33 3.36 2.21
Insulin lispro (Humalog)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	56.38 55.27 28.02	3.76 3.68 2.80
Humulin Regular	100 U/mL	5 × 3 mL cartridge 10 mL vial	45.12 22.99	3.01 2.30
Novolin ge Toronto	100 U/mL	5 × 3 mL cartridge 10 mL vial	43.30 22.06	2.89 2.21
Intermediate-acting human insulin				
Insulin isophane (Humulin NPH)	100 U/mL	5 × 3 mL cartridge 10 mL vial	45.12 22.99	3.01 2.30
Insulin isophane (Novolin ge NPH)	100 U/mL	5 × 3 mL cartridge 10 mL vial	44.34 22.56	2.96 2.26
Long-acting insulin analogues				
Insulin glargine (Lantus)	100 U/mL	5 × 3 mL cartridge 5 × 3 disposable pen 10 mL vial	92.85 92.85 61.69	6.19 6.19 6.17
Insulin detemir (Levemir)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	106.76 107.29	7.12 7.15
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 Formulary (July 2015).

APPENDIX 3: REVIEWER WORKSHEETS

TABLE 5: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug Product	Empagliflozin (Jardiance) 10 mg, 25 mg
Treatment	10 or 25 mg once daily
Comparators	Canagliflozin 100 mg or 300 mg, dapagliflozin 5 mg or 10 mg, sitagliptin 100 mg, saxagliptin 5 mg, linagliptin 5 mg, alogliptin 25 mg daily
Study Question	What is the cost of empagliflozin relative to other SGLT-2 inhibitors and DPP-4 inhibitors, as a third-line treatment of type 2 diabetes, from the perspective of a Canadian public payer?
Type of Economic Evaluation	Cost comparison (drug costs only)
Target Population	Patients with type 2 diabetes
Perspective	Canadian public payer
Outcome(s) Considered	A1C change from baseline Weight Systolic blood pressure Hypoglycemic events Urinary tract infections
Key Data Sources	
Cost	Ontario Drug Benefit, IMS Brogan DeltaPA
Clinical Efficacy	Manufacturer-conducted network meta-analysis
Harms	Manufacturer-conducted network meta-analysis
Time Horizon	One year
Results for Base Case	The cost of empagliflozin per patient per year is essentially identical to either canagliflozin or dapagliflozin as third-line treatment. Empagliflozin provides a cost-saving treatment option, up to $142.42 (with markup and dispensing fees included) per patient per year, compared with most DPP-4 inhibitors.

A1C = glycated hemoglobin; DPP = dipeptidyl peptidase; SGLT = sodium glucose cotransporter.

Manufacturer's Results

The submitted price for empagliflozin is essentially the same as the other two sodium glucose cotransporter (SGLT)-2 inhibitors and alogliptin, and is less costly than sitagliptin, the most commonly used of the currently marketed dipeptidyl peptidase-4 (DPP)-4 inhibitors. Compared with other DPP-4 inhibitors, empagliflozin is more costly than linagliptin, but less costly than saxagliptin (for the more common 5 mg dose) (Table 6).

TABLE 6: MANUFACTURER'S COST ANALYSIS

Drug/Comparator	Strength	Weights	Daily Drug Cost	Annual Drug Cost	Annual Drug Cost (+ Markup/Fee)[a,b]	Cost Differential
Jardiance (empagliflozin)[c]	10 mg or 25 mg	NA	$2.6177	$955.46	$1,139.33	NA
Primary comparator — SGLT-2 inhibitors (weights are based on equal distribution due to lack of data)						
SGLT-2 inhibitor class		100%	$2.6189	$955.88	$1,139.78	($0.42)
Invokana (canagliflozin)[d]	100 mg	25%	$2.6177	$955.46	$1,139.33	$0.00
	300 mg	25%	$2.6177	$955.46	$1,139.33	$0.00
Forxiga (dapagliflozin)[d]	5 mg	25%	$2.6200	$956.30	$1,140.24	($0.84)
	10 mg	25%	$2.6200	$956.30	$1,140.24	($0.84)
Secondary comparators — DPP-4 inhibitors (select source for weights in the box to the right)						
DPP-4 inhibitor class		100%	$2.8860	$1,053.39	$1,245.09	($97.93)
Januvia (sitagliptin)	25 mg	0.83%	$2.9790	$1,087.34	$1,281.75	($131.87)
	50 mg	3.25%	$2.9790	$1,087.34	$1,281.75	($131.87)
	100 mg	64.86%	$2.9790	$1,087.34	$1,281.75	($131.87)
Onglyza (saxagliptin)	2.5 mg	1.53%	$2.3997	$875.89	$1,053.39	$79.57
	5 mg	13.07%	$2.8753	$1,049.48	$1,240.87	($94.02)
Trajenta (linagliptin)	5 mg	16.45%	$2.5500	$930.75	$1,112.64	$24.71
Nesina (alogliptin)[d]	6.25 mg	0.00%	$2.6177	$955.46	$1,139.33	$0.00
	12.5 mg	0.00%	$2.6177	$955.46	$1,139.33	$0.00
	25 mg	0.00%	$2.6177	$955.46	$1,139.33	$0.00

DPP-4 = dipeptidyl peptidase-4; NA = not applicable; ODB = Ontario Drug Benefit; SGLT = sodium glucose cotransporter.
Prices are from the ODB formulary (April 2015) unless otherwise indicated.
[a] Based on ODB rules of 8% markup and $8.83 dispensing fee.
[b] Assumes a 30-days' claim.
[c] Price of empagliflozin is the manufacturer-submitted price.
[d] The prices of canagliflozin, dapagliflozin, and alogliptin are from IMS Brogan DeltaPA
Source: Adapted from the manufacturer pharmacoeconomic submission, page 16, Table 2 and worksheet cost minimization analysis of Pharmacoeconomic Evaluation.[3]

At the submitted price, the anticipated drug cost (excluding markup and dispensing fees) of empagliflozin is $995.46 per patient per year. Relative to other SGLT-2 inhibitors and DPP-4 inhibitors, empagliflozin resulted in:

- Approximately the same cost as other SGLT-2 inhibitors
- A cost differential of $97.93 per year compared with DPP-4 inhibitors, when looking at the weighted average cost of the DPP-4 inhibitor class
- A cost savings of $131.87 to an incremental cost of $79.57 per patient per year versus the individual DPP-4 inhibitors.

The manufacturer conducted sensitivity analyses with a decreased compliance rate of 80% and a weighted average cost of the DDP-4 inhibitor class based on all CDR-participating drug plans, instead of just the Ontario Drug Benefit (ODB) program. The sensitivity analyses demonstrated that these findings are robust.

CADTH Common Drug Review Results

The manufacturer had included the ODB markup and dispensing fees in drug cost presented in the pharmacoeconomic submission, which resulted in slightly greater cost differentials when comparing different drugs. Because of variation in markup and dispensing fees across Canada, CDR considered only drug costs in its reanalyses.

The submitted price for empagliflozin is approximately the same as canagliflozin, and is lower than that of sitagliptin, the most commonly used of the currently reimbursed DPP-4 inhibitors. Compared with other DPP-4 inhibitors, empagliflozin is more costly than linagliptin and alogliptin, but less costly than saxagliptin (for the more common 5 mg dose).

The manufacturer had submitted a weighted average cost of the SGLT-2 inhibitors by assuming equal market shares, and of the DDP-4 inhibitors based on claims data from Q1 to Q4 period in 2014 in Ontario. It is important to note that all doses were included in the manufacturer's calculations, despite the fact that sitagliptin (25 mg, 50 mg) and saxagliptin (2.5 mg) are typically used only in patients with renal insufficiency, whereas the product monograph for empagliflozin specifies that empagliflozin is not recommended for use in patients with renal insufficiency (estimated glomerular filtration rate < 45 mL/min/1.73 m^2). Thus, empagliflozin is unlikely to replace these lower DPP-4 doses.

More important, the differential between the price of empagliflozin and a weighted class average price does not imply a saving of that amount when empagliflozin is listed on the formulary. It would be true only if empagliflozin replaces the existing comparators in proportions exactly equal to their current market shares, which is highly unlikely.

As an illustration, CDR calculated the utilization of DPP-4 inhibitors in Ontario using claims data from Q1 2014 through Q1 2015 and estimated an updated weighted average price for this class with all doses included or with recommended doses only. Price data were obtained from the ODB. The results (Table 7) indicate that the price for empagliflozin is lower than that for saxagliptin (5 mg) and sitagliptin as well as the ODB weighted class average price. The cost differential between empagliflozin and the DPP-4 inhibitor class average is approximately the same, whether lower doses are included or not, as a result of counterbalancing effects of sitagliptin (25 mg and 50 mg) versus saxagliptin (2.5 mg). However, this result could change if the prices and/or shares of these lower doses change.

TABLE 7: CADTH COMMON DRUG REVIEW ANALYSIS OF PRICE FOR EMPAGLIFLOZIN

Drug/Comparator	Strength	Weights[a]	Daily Drug Cost	Annual Drug Cost	Cost Differential
Jardiance (empagliflozin)[b]	10 mg or 25 mg	NA	$2.6177	$955.46	NA
DPP-4 inhibitors					
Weighted market average (DPP-4 inhibitors — all doses)			$2.8837	$1,052.56	($97.10)
Weighted market average (DPP-4 inhibitors — recommended doses)			$2.8873	$1053.87	($98.41)
Januvia (sitagliptin)	25 mg	0.91%	$2.9790	$1,087.34	($131.87)
	50 mg	3.54%	$2.9790	$1,087.34	($131.87)
	100 mg	64.03%	$2.9790	$1,087.34	($131.87)
Onglyza (saxagliptin)	2.5 mg	1.57%	$2.3997	$875.89	$79.57
	5 mg	13.00%	$2.8753	$1,049.48	($94.02)
Trajenta (linagliptin)	5 mg	16.94%	$2.5500	$930.75	$24.71
Nesina (alogliptin)[c]	6.25 mg	0.00%	$2.1000	$766.50	$188.96
	12.5 mg	0.00%	$2.1000	$766.50	$188.96
	25 mg	0.00%	$2.1000	$766.50	$188.96

DPP = dipeptidyl peptidase; NA = not applicable; ODB = Ontario Drug Benefit.
Note: Prices are from the ODB formulary (June 2015) unless otherwise indicated.
[a] Based on the ODB claims data (Q1 2014 through Q1 2015) from IMS PharmaStat.
[b] Price of empagliflozin is the manufacturer-submitted price.
[c] Price of alogliptin is from the Quebec drug formulary (June 2015).

If empagliflozin is added to the existing drugs, there are two possible effects: an expansion of the market for the class, and substitution within the DPP-4 and SGLT-2 inhibitor classes. Many factors will have an impact on which and in what proportions existing drugs, in particular DPP-4 inhibitors, are going to be replaced by empagliflozin.

TABLE 8: KEY LIMITATIONS

Identified Limitation	Description	Implication
NMA limitations	Many comparators that were deemed relevant in the CDR review protocol were not included in the literature search, or, as for insulin and its analogues, results were not presented compared with empagliflozin. Additionally, the applicability of the NMA as a whole is less certain as appraisals of the included studies, details of the search strategy, and a list of excluded studies and/or a PRISMA statement were not provided. Most of the comparisons in the network of evidence were informed by a single trial. For safety outcomes, few events were reported by the studies. RCTs are generally powered to detect a difference for the primary efficacy outcome, but not for safety outcomes. Therefore, the heterogeneity of the estimates for hypoglycemic events was high. For genital tract infections, no NMA could be conducted because only one trial reported this adverse event.	There remains uncertainty over the treatment similarities, especially in secondary outcomes.
Relevant comparators were omitted	The manufacturer did not consider or report on insulin as a comparator, despite including insulin studies in the NMA. In addition, the manufacturer did not consider oral therapies in other drug classes that are less expensive than empagliflozin and used as third-line treatment of type 2 diabetes, such as acarbose or pioglitazone, although the latter is not frequently used because of safety issues.	The cost savings may be overestimated with the exclusion of other comparators from the base-case analysis.
Cost impact not properly estimated	Comparing the price of empagliflozin with a weighted average cost of the DDP-4 inhibitors based on claims data to estimate potential cost savings is not adequate. The differential between the price of empagliflozin and the weighted class average price does not imply a saving of that amount when empagliflozin is listed on the formulary. It would be true only if empagliflozin replaces the existing drugs in proportions exactly equal to their market shares, which is highly unlikely. The cost of likely market expansion associated with empagliflozin is ignored.	The economic analysis does not provide an adequate assessment of the cost impact of empagliflozin.

CDR = CADTH Common Drug Review; DDP = dipeptidyl peptidase; NMA = network meta-analysis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial.

REFERENCES

1. [Pr]Jardiance (empagliflozin): 10 mg and 25 mg tablets [draft product monograph]. Burlington (ON): Boehringer Ingelheim; 2014 Aug 27.
2. CDR submission: Jardiance™ (empagliflozin), 10 mg and 25 mg tablets. Company: Boehringer Ingelheim [**CONFIDENTIAL** manufacturer's submission]. Burlington (ON): Boehringer Ingelheim; 2015 May 1.
3. Pharmacoeconomic evaluation. In: CDR submission: Jardiance™ (empagliflozin), 10 mg and 25 mg tablets. Company: Boehringer Ingelheim [**CONFIDENTIAL** manufacturer's submission]. Burlington (ON): Boehringer Ingelheim; 2015 May 1.
4. Comparative efficacy and safety of empagliflozin with other antidiabetic drugs for the third-line treatment of type-2 diabetes mellitus [**CONFIDENTIAL** internal manufacturer's report]. Version 3. Vancouver: Redwood Outcomes; 2015 Apr 19.
5. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index [Internet]. Toronto: The Ministry; 2015. [cited 2015 Jul 27]. Available from: https://www.healthinfo.moh.gov.on.ca/formulary/
6. Common Drug Review. Canagliflozin (Invokana - Janssen Inc). Indication: type 2 diabetes mellitus [Internet]. Ottawa: CADTH; 2015. (CDEC final recommendation). [cited 2015 Jul 23]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0370_Invokana_Jan-19_15.pdf
7. List of medications [Internet]. Quebec (QC): Régie de l'assurance maladie du Quebec (RAMQ); 2015. [cited 2015 Jul 27]. Available from: https://www.prod.ramq.gouv.qc.ca/DPI/PO/Commun/PDF/Liste_Med/Liste_Med/liste_med_2015_03_16_en.pdf