

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

ERTUGLIFLOZIN (STEGLATRO)

(Merck Canada Inc.)

Indication: Type 2 Diabetes Mellitus

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Abbreviations

A1C	glycated hemoglobin
CDR	CADTH Common Drug Review
DPP-4	dipeptidyl peptidase-4
FDC	fixed-dose combination
GLP-1	glucagon-like peptide-1
NMA	network meta-analysis
SGLT2	sodium-glucose cotransporter-2
T2DM	type 2 diabetes mellitus

Drug	Ertugliflozin (Steglatro)
Indication	<p>Monotherapy: for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.</p> <p>Add-on combination: indicated in adult patients with type 2 diabetes mellitus to improve glycemic control in combination with:</p> <ul style="list-style-type: none"> • metformin, • metformin and sitagliptin, <p>when the therapy listed above, along with diet and exercise, does not provide adequate glycemic control.</p>
Reimbursement Request	<p>As monotherapy for patients who have inadequate glycemic control and for whom metformin or a sulfonylurea is inappropriate due to contraindications or intolerance.</p> <p>Add-on to metformin for patients who have inadequate glycemic control on metformin and have a contraindication or intolerance to a sulfonylurea.</p>
Dosage Form	5 mg and 15 mg oral tablets
NOC Date	May 9, 2018
Manufacturer	Merck Canada Inc.

Executive Summary

Background

Ertugliflozin is an oral antidiabetic drug belonging to the sodium-glucose cotransporter-2 (SGLT2) inhibitor class. It is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM) for whom metformin is inappropriate due to contraindications or intolerance; and adjunct to diet and exercise to improve glycemic control in adult patients with T2DM inadequately controlled on metformin alone or metformin and sitagliptin¹. The manufacturer is seeking reimbursement as monotherapy for patients with T2DM who have inadequate glycemic control and for whom metformin or a sulfonylurea is inappropriate due to contraindications or intolerances, and as an add-on therapy to metformin in patients who have inadequate glycemic control and have a contraindication or intolerance to sulfonylurea.

The recommended starting dose of ertugliflozin is 5 mg, taken once daily in the morning with or without food. The daily dose may be increased to a maximum of 15 mg if additional glycemic control is needed.¹ The manufacturer submitted ertugliflozin at a price of \$2.45 per tablet for both 5 mg and 15 mg doses, or an annual cost of \$894 per patient.²

CADTH Common Drug Review (CDR) is currently reviewing ertugliflozin as part of a fixed-dose combination with metformin which is indicated as an adjunct to diet and exercise alone, or in combination with sitagliptin, for those patients with T2DM who are inadequately controlled on metformin, or metformin and sitagliptin; or for patients who are on the individual components (ertugliflozin and metformin).

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a comparison of daily costs of ertugliflozin to other SGLT2 inhibitors: canagliflozin (Invokana), dapagliflozin (Forxiga), and empagliflozin (Jardiance). The perspective was that of a Canadian public drug payer.²

Currently no head-to-head comparisons have been conducted to compare the treatment effects of ertugliflozin to SGLT2s. In the absence of direct comparisons, two manufacturer-sponsored network meta-analyses (NMAs) were submitted to assess the comparative efficacy and safety of ertugliflozin to other SGLT2 inhibitors, as well as placebo for the treatment of T2DM in two populations of interest: patients uncontrolled on diet and exercise (monotherapy) and those uncontrolled on metformin and those uncontrolled on metformin and a dipeptidyl peptidase-4 (DPP4) inhibitor.³ The NMAs were based on a systematic literature review conducted by the manufacturer, which identified relevant randomized controlled trials, which was then synthesized using a Bayesian NMA (fixed- and random-effect models) to estimate treatment effects on a number of outcomes. In the NMAs, the lower and higher doses of ertugliflozin (5 mg and 15 mg) were compared with the relative lower and higher doses of canagliflozin (100 mg and 300 mg), dapagliflozin (5 mg and 15 mg), and empagliflozin (10 mg and 35 mg), as well as placebo. Key outcomes analyzed were changes in body weight, blood pressure, and A1C, while other outcomes (lipids and estimated glomerular filtration rate) were considered but not reported in every study. The manufacturer concluded that there were no significant differences in A1C between low-dose ertugliflozin and other SGLT2 agents while the higher dose (15 mg) of ertugliflozin significantly reduced A1C and blood pressure compared with relative doses of dapagliflozin (10 mg) and empagliflozin (25 mg). Overall the manufacturer-sponsored NMA concluded that both doses of ertugliflozin were comparable on efficacy and safety outcomes to SGLT2 at assumed relative doses.²

The manufacturer reported the daily cost of ertugliflozin at \$2.45, which would result in a cost savings of \$0.17 to \$0.31 compared with empagliflozin (\$2.62 per 10 mg dose or 25 mg daily) and canagliflozin (\$2.62 per 100 mg per tablet or \$2.76 per 300 mg daily), and be cost-neutral or cost-saving compared with dapagliflozin depending on the dose used (\$2.45 per 5 mg tablet or \$2.62 per 10 mg tablet).²

Key Limitations

Uncertain comparative clinical effectiveness: The CDR Clinical Review indicated that the restrictions placed on the inclusion criteria, specifically relating to the comparators (SGLT2 only) and study design (follow-up period of 24 to 26 weeks), reduce the sample size, which may increase the chance of a conclusion of equivalent efficacy or safety, and thus limit the utility and robustness of the results. No head-to-head trials comparing ertugliflozin to other SGLT2 inhibitors have been conducted which may limit the conclusion that ertugliflozin is clinically effective compared with other SGLT2 inhibitors, due to the observational nature of NMA data and evidence synthesis. The CDR Clinical Report identified one study that included sitagliptin (a DPP-4 inhibitor), although no comparisons were made between the ertugliflozin and sitagliptin monotherapy treatment groups, as well as another study comparing ertugliflozin to glimepiride (a sulfonylurea). No other studies were identified directly comparing ertugliflozin to other DPP-4 inhibitors, sulfonylureas, or glucagon-like peptide-1 (GLP-1) receptor agonists. The findings of these studies indicated that ertugliflozin 15 mg may be noninferior to glimepiride, but that ertugliflozin 5 mg may not

be noninferior to glimepiride. The CDR Clinical Report identified studies that assessed ertugliflozin, with or without other agents, compared with placebo, with or without other agents; finding that ertugliflozin, with or without other agents, was associated with statistically significant benefits compared with placebo.

Additional pricing and cost for combination therapy: The daily cost of ertugliflozin therapy may increase if a patient is taking ertugliflozin in combination with sitagliptin (as per the Health Canada–approved indication). The manufacturer did not consider this in the submitted NMA and economic evaluation. Sitagliptin alone costs \$3.10 per day.⁴ If ertugliflozin is used in combination with sitagliptin, the cost to the health care system may be increased (relative to ertugliflozin in combination with metformin). Other SGLT2 inhibitors may also be co-administered with other treatments that may result in similar total treatment costs.

Exclusion of relevant comparators: The manufacturer did not take into account relevant comparators like DPP-4 inhibitors and other antihyperglycemic medications that ertugliflozin may displace. The NMA submitted by the manufacturer only compared ertugliflozin to SGLT2 inhibitors. The CDR Clinical Review identified two studies that directly compared ertugliflozin to glimepiride and sitagliptin. However, no other studies have compared ertugliflozin and other second-line treatment therapy drugs for T2DM.

Type of analysis may not be appropriate: Given the limitations associated with the comparative effectiveness and included comparators, CDR considered that a cost-utility analysis may have been more appropriate to assess the comparative costs and effects of ertugliflozin with or without metformin compared with relevant comparator treatments.

Issues for Consideration

Differential pricing: The publicly available prices of comparators may differ across provinces, thus impacting the manufacturer’s estimated cost savings. As per the indication, ertugliflozin may be used in combination with sitagliptin to achieve better glycemic control. However, the manufacturer did not provide an estimate of additional costs associated with the use of sitagliptin, which might impact the costs and estimated savings stated in the manufacturer’s economic evaluation.

Results/Conclusions

The CDR clinical reviewers concluded that ertugliflozin as monotherapy or as add-on therapy was more effective than placebo; that ertugliflozin may have similar efficacy to other SGLT2 inhibitors (but caution should be used when interpreting the results due to limited evidence and the robustness of results with the NMA); and that, although ertugliflozin 15 mg was noninferior to glimepiride, noninferiority was not met for ertugliflozin 5 mg versus glimepiride, as the upper bound of the 95% confidence interval for the difference between groups was not below 0.3%.

At the current daily cost of \$2.45, ertugliflozin is less costly, or equivalent in cost, to other publicly available SGLT2 inhibitors. If price negotiations have occurred, this will affect any anticipated cost savings of ertugliflozin compared with other treatments within the same drug class.

Ertugliflozin is more costly than sulfonylureas, other older treatments (e.g., meglitinides or thiazolidinediones), and at least one DPP-4 inhibitor, but is less costly than GLP-1 receptor agonists based on available prices.

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 from the Ontario Drug Benefit (ODB) Formulary,⁴ 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 Non-Insulin Antidiabetic Agents

Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Ertugliflozin (Steglatro)	5 mg 15 mg	Tablet	2.4500^a	5 mg or 15 mg daily	2.45	894
SGLT2 inhibitors						
Empagliflozin (Jardiance)	10 mg 25 mg	Tablet	2.6177	10 mg or 25 mg daily	2.62	955
Canagliflozin (Invokana)	100 mg 300 mg	Tablet	2.7627	100 mg or 300 mg daily	2.76	1,007
Dapagliflozin (Forxiga)	5 mg 10 mg	Tablet	2.6750	5 mg or 10 mg daily	2.68	976
SGLT2 inhibitors plus metformin fixed-dose combinations						
Dapagliflozin/metformin (Xigduo)	5 mg + 850 mg or 1,000 mg	Tablet	1.2250	Two tablets daily	2.45	894
Canagliflozin/metformin (Invokamet)	50 mg & 500 mg, 850 mg, or 1,000 mg 150 mg & 500 mg, 850 mg or 1,000 mg	Tablet	1.5660 ^c	Two tablets daily	3.13	1,143
Empagliflozin/metformin (Synjardy)	5 mg & 500 mg, 850 mg or 1,000 mg 12.5 mg & 500 mg, 850 mg or 1,000 mg	Tablet	1.3783 ^c	Two tablets daily	2.76	1,006
Biguanides						
Metformin (generics)	500 mg 850 mg	Tablet	0.0247 0.0339 ^b	500 mg three to four times daily 850 mg two to three times daily	0.07 to 0.10	27 to 36
	500 mg 1,000 mg	ER Tablet	0.6068 ^c 1.2196 ^c	1,000 mg to 2,000 mg once a day	1.22 to 2.44	445 to 890

Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
DPP-4 inhibitors						
Sitagliptin (Januvia)	25 mg 50 mg 100 mg	Tablet	3.0932	100 mg daily	3.09	1,129
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	Tablet	2.4760 2.9680	5 mg daily	2.48 2.97	904 to 1,083
Linagliptin (Trajenta)	5 mg	Tablet	2.5500	5 mg daily	2.55	931
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	Tablet	2.2000 ^c	25 mg daily	2.20	803
DPP-4 inhibitor plus metformin fixed-dose combinations						
Alogliptin/metformin (Kazano)	12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg	Tablet	1.1950 ^c	Two tablets daily	2.39	872
Linagliptin/metformin (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	Tablet	1.3337	Two tablets daily	2.67	974
Saxagliptin/metformin (Kombiglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	Tablet	1.2700	Two tablets daily	2.54	927
Sitagliptin/metformin (Janumet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg	Tablet	1.6779	Two tablets daily Max daily dose: 100 mg (sitagliptin) and 2,000 mg (metformin)	3.36	1,225
	50 mg/500 mg	ER Tablet	1.6433	Once daily Max daily dose:	1.64 to 3.28	600 to 1,200
	50 mg/1,000 mg	ER Tablet	1.6779	100 mg (sitagliptin) and 2,000 mg (metformin)	1.68 to 3.36	613 to 1,225
	100 mg/1,000 mg	ER Tablet	3.3557		3.36	1,225
GLP-1 receptor agonist						
Lixisenatide (Adlyxine)	10 mcg 20 mcg	14 dose pre-filled pen (3 mL)	56.9800 ^c	Starting dose of 10 mcg once daily for 14 days, after which the dose should be increased to 20 mcg once daily	4.07	1,486
Dulaglutide (Trulicity)	0.75 mg/0.5 mL 1.5 mg/0.5 mL	4 x 0.5 mL pre-filled pen	49.7900 ^c	0.75 mg to 1.5 mg once weekly	7.11	2,596
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/mL)	119.7250 ^c per mL	5 mcg to 10 mcg twice daily	4.79	1,748
Exenatide (Bydureon)	2 mg	2 mg pre-filled pen	49.4850 ^c	2 mg once weekly	7.07	2,580
Liraglutide (Victoza)	2 mL x 3 mL 3 mL x 3 mL	Pre-filled pen injection (6mg/mL)	29.0133 ^c per mL	1.2 mg to 1.8 mg daily	5.80 to 8.70	2,118 to 3,177
Sulfonylureas						

Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
Gliclazide	80 mg	Tablet	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 (Diamicon MR)	30 mg 60 mg	SR tablet ER tablet	0.0931 0.0632	30 mg to 120 mg daily	0.03 to 0.13	22 to 46
Glimepiride (generics)	1 mg 2 mg 4 mg	Tablet	0.4900	1 mg to 4 mg daily	0.49	179
Glyburide (generics)	2.5 mg 5.0 mg	Tablet	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
TZDs						
Pioglitazone (generics)	15 mg 30 mg 45 mg	Tablet	0.3800 ^{b,d} 0.5360 ^{b,d} 0.8075 ^{b,d}	15 mg to 45 mg daily	0.38 to 0.81	139 to 295
Rosiglitazone (Avandia, generics)	2 mg 4 mg 8 mg	Tablet	1.1692 1.8346 2.6235	4 mg to 8 mg daily	1.17 to 2.62	427 to 956
Meglitinides						
Repaglinide	0.5 mg 1 mg 2 mg	Tablet	0.2083 0.2165 0.2441	0.5 mg to 2 mg daily	0.21 to 0.24	76 to 89
Alpha-glucosidase inhibitors						
Acarbose (Glucobay)	50 mg 100 mg	Tablet	0.2695 0.3732	50 mg to 100 mg 3 times daily	0.81 to 1.12	295 to 409

DPP-4 = dipeptidyl peptidase-4; ER = extended release; GLP-1 = glucagon-like peptide-1; MR = modified release; SGLT2 = sodium-glucose cotransporter-2; TZD = thiazolidinediones.

Note: Rosiglitazone (Avandia) was reimbursed on other drug formularies at higher prices (e.g., on the Saskatchewan and Alberta drug formularies, rosiglitazone is reimbursed at \$1.03 per 2 mg tablet, \$1.62 per 4 mg tablet, and \$2.32 per 8 mg tablet).

^a Manufacturer's submission price.⁵

^b Saskatchewan Drug Formulary (May 2018).⁶

^c IMS DeltaPA – IMS Brogan (May 2018).⁷

^d Pioglitazone was reimbursed on the ODB Formulary, but with "off-formulary interchangeable" prices, thus the Saskatchewan prices were used. The "off-formulary interchangeable" prices listed are \$1.2250 per 15 mg tablet, \$1.5716 per 30 mg tablet, and \$3.3105 per 45 mg tablet).

Source: ODB Formulary (May 2018) prices, unless otherwise indicated.⁴

Appendix 1: Price Reduction Analysis

As the manufacturer’s submission did not report on the costs of other drug classes for type 2 diabetes mellitus (T2DM), CADTH Common Drug Review (CDR) quantified the extent to which the price of ertugliflozin would need to be reduced to be considered cost-neutral to the lowest cost drug in each drug class for T2DM. For example, dipeptidyl peptidase-4 inhibitors (DPP-4s) are considered a common therapy for T2DM. The price of the lowest cost DPP-4, alogliptin, is \$2.20; at that price, ertugliflozin would need to be reduced by 10% to be considered cost-neutral compared with alogliptin (Table 3). The price of ertugliflozin is reported from the manufacturer’s submission,⁵ while all other reported costs are from the ODB Formulary,⁴ unless otherwise specified.

Table 2: CDR Analysis for Price Reduction Scenarios for Ertugliflozin

Scenario	Current Price of Ertugliflozin	Reduction Needed to Equal Comparator	Comparator Cost
Price reduction needed to equal least expensive DPP- 4 (alogliptin)	\$2.45	10%	\$2.20 ^a
Price reduction needed to equal least expensive sulfonylurea (glyburide)		99%	\$0.03
Price reduction needed to equal least expensive TZD (pioglitazone)		84%	\$0.38
Price reduction needed to equal least expensive alpha-glucosidase inhibitor (acarbose)		64%	\$0.87

DPP-4: dipeptidyl peptidase-4 inhibitor; TZD: thiazolidinediones.

Source: IMS DeltaPA – IMS Brogan (May 2018).⁷

Appendix 2: Reviewer Work Sheets

Table 3: Summary of Manufacturer’s Submission

Drug Product	Ertugliflozin (Steglatro)
Treatment	Ertugliflozin (Steglatro)
Comparator(s)	Canagliflozin Dapagliflozin Empagliflozin
Study Question	“Is ertugliflozin a cost-effective alternative to currently available SGLT2 drugs, in patients with T2DM who have access to SGLT2 therapy?”
Type of Economic Evaluation	Cost comparison
Target Population	Adults with T2DM who would otherwise be treated using an SGLT2 as monotherapy based on current plan reimbursement criteria.
Perspective	Canadian public drug payer
Outcome Considered	Drug costs
Key Data Sources	
Cost	Drug costs were obtained from the Ontario Drug Benefit Formulary and the manufacturer’s submitted price.
Clinical Efficacy	Manufacturer-sponsored NMA comparing treatment efficacy of ertugliflozin to empagliflozin, canagliflozin, and dapagliflozin.
Harms	Not considered
Time Horizon	None
Results for Base Case	The manufacturer submitted ertugliflozin at a daily cost of \$2.45 providing a cost savings of \$0.17 to \$0.31 compared with both doses of empagliflozin (\$2.62 per tablet per day) and canagliflozin (\$2.62 per 100 mg tablet or \$2.76 per 300 mg tablet) while being cost-neutral to cost-saving compared with dapagliflozin (\$2.45 per 5 mg tablet or \$2.62 per 10 mg tablet).

NMA = network meta-analysis; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

Source: Manufacturer’s pharmacoeconomic submission.

Manufacturer's Results

The manufacturer submitted a cost comparison comparing the daily cost of ertugliflozin to other sodium-glucose cotransporter-2 (SGLT2) inhibitors. This form of analysis was chosen based on the manufacturer's assumption of equivalent efficacy, supported by the network meta-analysis (NMA) indirectly comparing ertugliflozin and other SGLT2 inhibitors. The daily cost of ertugliflozin was based on list prices and recommended dosage approved by Health Canada. Health Canada approved two strengths of each SGLT2 inhibitor and the manufacturer compared both doses of each drug to the equivalent dose of ertugliflozin. A discount rate was not applied due to the type of economic evaluation submitted. The manufacturer considered the costs associated with the dispensing of prescriptions and assumed a 30-day prescription would be appropriate. The manufacturer's results from the cost comparison are outlined in Table 4. Overall, the manufacturer deemed ertugliflozin to be cost-effective compared with other SGLT2 agents available in Canada, generating savings of \$0.17 to \$0.31 per day compared with empagliflozin and canagliflozin, while being cost-neutral compared with dapagliflozin.

Table 4: Manufacturer-Reported Results

Therapy	Strengths	Daily Dosage	Drug Cost per Day	Total Cost per Day	Daily Cost vs. Comparator
Ertugliflozin (Steglatro)	5 mg 15 mg	1 unit	\$2.45	\$2.74	
Empagliflozin (Jardiance)	10 mg 25 mg	1 unit	\$2.62	\$2.91	\$0.17
Canagliflozin (Invokana)	100 mg 300 mg	1 unit	\$2.62 to \$2.76	\$2.91 to \$3.06	\$0.17 to \$0.31
Dapagliflozin (Forxiga)	5 mg 10 mg	1 unit	\$2.45 to \$2.62	\$2.74 to \$2.91	\$0.00 to \$0.17

Source: Manufacturer's pharmacoeconomic submission.²

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