



CADTH

# Common Drug Review

## *Pharmacoeconomic Review Report*

September 2017

<b>Drug</b>	Empagliflozin and Metformin Fixed-Dose Combination (Synjardy)
<b>Indication</b>	<p>SYNJARDY (empagliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on:</p> <ul style="list-style-type: none"><li>• metformin</li><li>• sulfonylurea in combination with metformin</li><li>• pioglitazone in combination with metformin</li><li>• insulin in combination with metformin</li></ul> <p>Or in patients already being treated and achieving glycemic control with:</p> <ul style="list-style-type: none"><li>• metformin and empagliflozin as separate tablets</li><li>• sulfonylurea in combination with metformin and empagliflozin as separate tablets</li><li>• pioglitazone in combination with metformin and empagliflozin as separate tablets</li><li>• insulin in combination with metformin and empagliflozin as separate tablets</li></ul>
<b>Reimbursement request</b>	As an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus already stabilized on therapy with metformin and empagliflozin, to replace the individual components of metformin and empagliflozin in these patients.
<b>Dosage form</b>	5 mg / 500 mg, 5 mg / 850 mg, 5 mg / 1,000 mg, 12.5 mg / 500 mg, 12.5 mg / 850 mg, 12.5 mg / 1,000 mg, tablets for oral administration
<b>NOC date</b>	July 29, 2016
<b>Manufacturer</b>	Boehringer Ingelheim (Canada) Ltd.

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## **ABBREVIATIONS**

<b>ALO</b>	alogliptin
<b>CANA</b>	canagliflozin
<b>CDR</b>	CADTH Common Drug Review
<b>DAPA</b>	dapagliflozin
<b>DPP-4</b>	dipeptidyl peptidase-4
<b>EMPA</b>	empagliflozin
<b>FDC</b>	fixed-dose combination
<b>LINA</b>	linagliptin
<b>MET</b>	metformin
<b>SAXA</b>	saxagliptin
<b>SITA</b>	sitagliptin
<b>SGLT2</b>	sodium-glucose cotransporter-2
<b>SU</b>	sulfonylurea
<b>T2DM</b>	type 2 diabetes mellitus

## SUMMARY

### Background

Empagliflozin (EMPA)/metformin (MET) fixed-dose combination (FDC) tablet (Synjardy) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM) inadequately controlled on MET alone, MET and a sulfonylurea (SU), MET and pioglitazone (PIO), or MET and insulin; or when EMPA and MET are already being co-administered as separate tablets with or without an SU, PIO, or insulin. The manufacturer is seeking reimbursement for adult patients with T2DM who are already stabilized on therapy with MET and EMPA, to replace the individual components.

EMPA/MET FDC is taken twice daily and is available in strengths of 5 mg or 12.5 mg EMPA plus 500 mg, 850 mg, or 1,000 mg MET. The manufacturer has submitted the anticipated market price of \$1.3500 per tablet, or \$2.70 per day, for all six strengths.

The CADTH Common Drug Review (CDR) previously reviewed EMPA (Jardiance), resulting in a CADTH Canadian Drug Expert Committee (CDEC) recommendation that it be reimbursed when added to MET and an SU in patients with T2DM with inadequate glycemic control for whom insulin is not an option.<sup>1</sup> EMPA is also currently under review by CDR for the treatment of patients with T2DM at high cardiovascular risk.<sup>2</sup> CDR has recently reviewed two other FDC products containing a sodium-glucose cotransporter-2 (SGLT2) inhibitor plus MET.<sup>3,4</sup>

### Summary of the economic analysis submitted by the manufacturer

The manufacturer submitted an analysis comparing the annual cost of EMPA/MET FDC with that of equivalent free-dose combinations of its individual components as the primary analysis, of other SGLT2 inhibitor/MET combinations as a secondary analysis, and of dipeptidyl peptidase-4 (DPP-4) inhibitor/MET combinations as a tertiary analysis.<sup>5</sup> The perspective was that of a Canadian public drug payer, and the time horizon was one year.

The manufacturer reported that the annual cost of EMPA/MET FDC, including an 8% markup and an \$8.83 dispensing fee every 30 days, is \$1,172 per patient, which is \$110 to \$145 less expensive than individually dosed EMPA and MET (\$1,282 to \$1,317 per patient per year). EMPA/MET FDC is also less expensive than other free-dose combinations of an SGLT2 inhibitor and MET (\$1,307 to \$1,330 per patient per year), but \$32 more expensive than dapagliflozin (DAPA)/MET FDC (\$1,140 per patient per year). The relative cost of EMPA/MET FDC to canagliflozin (CANA)/MET FDC could not be determined because of the lack of a publicly available price for the latter product at the time of the manufacturer's submission. When compared with DPP-4 inhibitor plus MET combinations, EMPA/MET FDC is more expensive than saxagliptin (SAXA)/MET FDC and linagliptin (LINA)/MET FDC, but less expensive than sitagliptin (SITA)/MET FDC, alogliptin (ALO)/MET FDC, and all free-dose combinations of a DPP-4 and MET.

### Key limitations

#### Average drug cost calculation inappropriate

The method used by the manufacturer to estimate the annual cost of free-dose combination comparators in effect assumes a uniform patient distribution across included dose combinations, which is unlikely to reflect actual practice. Additionally, some comparator dosing options were omitted, and, when introduced as part of CDR reanalyses, average costs shifted in some cases. In the absence of data

on real-world utilization across dose combinations, CDR reanalyses reported a range of annual costs for each free-dose combination rather than a point estimate.

### Missing comparator dosing options

The manufacturer's analysis did not include the 50 mg/850 mg and 150 mg/850 mg doses of CANA/MET FDC (Invokamet), and these dose combinations were also left out of the CANA plus MET free-dose combinations. The manufacturer also included only free-dose combinations for which there was an equivalent-dose FDC product, rather than all dose combinations within the recommended dose ranges of the products in question. This fails to consider that flexibility is an advantage of free-dose combinations when the comparable FDC product has more limited dosing options. CDR reanalyses therefore included the 1,000 mg, 1,700 mg, and 2,000 mg daily doses of MET and included all product monograph–recommended daily doses of the DPP-4 inhibitor or SGLT2 inhibitor in question for all free-dose combinations, regardless of whether those daily doses are available as an FDC product.

### Overestimation of pharmacy fee savings

The use of an FDC product typically provides savings because of the need for fewer professional pharmacy fees per claim. The manufacturer assumed a 30-day supply per claim in its base case. A larger days' supply is likely appropriate for many patients on stable doses of antidiabetes medications, given the chronic nature of the condition. CDR reviewers therefore recalculated the incremental costs or savings of EMPA/MET FDC versus the various comparators, assuming dispensing fees every 100 days, as well as without dispensing fees or markup. This reduced the magnitude of annual savings associated with the use of EMPA/MET FDC compared with the values reported by the manufacturer.

### Assumption of clinical similarity

Clinical similarity of EMPA/MET FDC to the free-dose combination was assumed on the basis of four phase I, single-administration studies in healthy volunteers, which demonstrated that EMPA/MET FDC is bioequivalent to the individual components administered separately based on commonly accepted criteria (CDR Clinical Report, Appendix 5). While there are no head-to-head trials comparing EMPA with other SGLT2 inhibitors, a network meta-analysis submitted by the manufacturer as part of the EMPA submission to CDR suggested that EMPA has efficacy similar to other SGLT2 inhibitors and DPP-4 inhibitors.<sup>1</sup> However, CDEC noted that there were no direct or indirect comparisons assessing the comparative efficacy of EMPA versus other antihyperglycemic drugs for the prevention of macrovascular and microvascular diabetes-related complications.<sup>1</sup>

### Issues for consideration

#### Potential use in treatment-naive patients with type 2 diabetes mellitus

The FDA recently approved the use of EMPA/MET FDC for the treatment of adults with T2DM who are treatment-naive.<sup>6</sup> While this indication is not approved in Canada, it is possible that some physicians may prescribe the EMPA/MET FDC as first-line therapy in future, particularly if the product is listed in an open fashion without eligibility criteria. EMPA/MET FDC is substantially more expensive than MET alone or an SU with or without MET, and its cost-effectiveness in a treatment-naive population has not been established. See Appendix 2 for the annual costs of non-insulin drugs for T2DM, which were not included in the main analyses.

### Results and conclusions

According to CDR's reanalysis, when dispensing fees and markup were excluded, the annual cost of EMPA/MET FDC (\$986 per patient) was \$2 to \$35 (0% to 3%) per patient less than that of its individual components (\$988 to \$1,020 per patient). EMPA/MET FDC was less expensive than CANA/MET FDC,

free-dose combinations of DAPA or CANA plus MET, SITA/MET FDC, and ALO/MET FDC, and all DPP-4 inhibitor plus MET free-dose combinations with the exception of 5 mg LINA plus 1,000 mg MET daily, but was 3%, 6%, and 1% more expensive than DAPA/MET FDC, SAXA/MET FDC, and LINA/MET FDCs, respectively. Use of EMPA/MET FDC would also save one dispensing fee per claim over its individual components or free-dose combinations of other comparators.

**Cost-comparison table**

The clinical expert consulted by CDR deemed the comparator treatments presented in Table 1 to be appropriate. Costs are manufacturer’s list prices, unless otherwise specified. Existing product listing agreements are not reflected in Table 1 and as such may not represent the actual costs to public drug plans.

**TABLE 1: COST-COMPARISON TABLE FOR COMBINATIONS OF SODIUM-GLUCOSE COTRANSPORTER-2 OR DIPEPTIDYL PEPTIDASE-4 INHIBITORS WITH METFORMIN**

Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
<b>EMPA/MET FDC (Synjardy)</b>	<b>5 mg/500 mg 5 mg/850 mg 5 mg/1,000 mg 12.5 mg/500 mg 12.5 mg/500 mg 12.5 mg/1,000 mg</b>	<b>Tab</b>	<b>1.3500<sup>a</sup></b>	<b>1 tablet twice daily</b>	<b>2.70</b>	<b>986</b>
<b>Free-dose combinations of EMPA and MET</b>						
EMPA plus MET (Jardiance plus generic)	10 mg 25 mg	Tab	2.6200	10 mg or 25 mg once daily	2.71 to 2.80	989 to 1,020
	500 mg 850 mg	Tab	0.0444 0.0610 <sup>b</sup>	1,000 to 2,000 mg daily in divided doses		
<b>Other SGLT2 inhibitor plus MET FDCs</b>						
DAPA/MET (Xigduo)	5 mg/850 mg 5 mg/1,000 mg	Tab	1.3100	1 tablet twice daily	2.62	956
CANA/MET (Invokamet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg 150 mg/ 500 mg 150 mg/850 mg 150 mg/100 mg	Tab	1.5338 <sup>c</sup>	1 tablet twice daily	3.07	1,120
<b>Free-dose combinations of other SGLT2 inhibitors and MET</b>						
DAPA plus MET (Forxiga plus generic)	5 mg 10 mg	Tab	2.6200	5 mg or 10 mg once daily	2.71 to 2.80	989 to 1,020
	500 mg 850 mg	Tab	0.0444 0.0610 <sup>b</sup>	1,000 mg to 2000 mg daily in divided doses		

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Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
CANA plus MET (Invokana plus generics)	100 mg 300 mg	Tab	2.6960	100 mg or 300 mg once daily	2.78 to 2.87	1,016 to 1,049
	500 mg 850 mg	Tab	0.0444 0.0610 <sup>b</sup>	1,000 mg to 2,000 mg daily in divided doses		
<b>DPP-4 inhibitor plus MET FDCs</b>						
SITA/MET FDC (Janumet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg	Tab	1.62	1 tablet twice daily	3.23	1,180
SAXA/MET FDC (Komboglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	Tab	1.27	1 tablet twice daily	2.54	927
LINA/MET FDC (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	Tab	1.3337	1 tablet twice daily	2.67	974
ALO/MET FDC (Kazano)	12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg	Tab	1.3700 <sup>c,d</sup>	1 tablet twice daily	2.74	1,000
<b>Free-dose combinations of DPP-4 inhibitors and MET</b>						
SITA plus MET (Januvia plus generics)	25 mg 50 mg 100 mg	Tab	2.9790	100 mg once daily	3.07 to 3.16	1,120 to 1,152
	500 mg 850 mg	Tab	0.0444 0.0610 <sup>b</sup>	1,000 mg to 2,000 mg daily in divided doses		
SAXA plus MET (Onglyza plus generics)	2.5 mg 5 mg	Tab	2.3997	5 mg once daily	2.96 to 3.05	1,082 to 1,114
	500 mg 850 mg	Tab	0.0444 0.0610 <sup>b</sup>	1,000 mg to 2,000 mg daily in divided doses		
LINA plus MET (Trajenta plus generics)	5 mg	Tab	2.5500	5 mg once daily	2.64 to 2.73	963 to 996
	500 mg 850 mg	Tab	0.0444 0.0610 <sup>b</sup>	1,000 mg to 2,000 mg daily in divided doses		
ALO plus MET (Nesina plus generics)	6.25 mg 12.5 mg 25 mg	Tab	2.6177 <sup>c,d</sup>	25 mg once daily	2.71 to 2.80	988 to 1,020

## CDR PHARMACOECONOMIC REVIEW REPORT FOR SYNJARDY

Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
	500 mg 850 mg	Tab	0.0444 0.0610 <sup>c,d</sup>	1,000 mg to 2,000 mg daily in divided doses		

ALO = alogliptin; CANA = canagliflozin; DAPA = dapagliflozin; DPP-4 = dipeptidyl peptidase-4; EMPA = empagliflozin; FDC = fixed-dose combination; LINA = linagliptin; MET = metformin; SAXA = saxagliptin; SGLT2 = sodium-glucose cotransporter-2; SITA = sitagliptin; Tab = tablet.

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

<sup>b</sup> Saskatchewan Formulary (July 2016).

<sup>c</sup> Delta PA, manufacturer's list price, accessed July 2016.

<sup>d</sup> Kazano is listed on the Régie de l'assurance maladie du Québec List of Medications at \$1.1450 per tablet, while Nesina is listed at \$2.1000 per tablet.

Source: Ontario Drug Benefit Formulary list prices (July 2016) unless otherwise indicated.

## APPENDIX 1: REVIEWER WORKSHEETS

TABLE 2: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug Product	EMPA/MET FDC (Synjardy)
Treatment	EMPA/MET FDC
Comparator(s)	EMPA plus MET as individual components DAPA/MET FDC CANA/MET FDC DAPA plus MET as individual components CANA plus MET as individual components SITA/MET FDC SAXA/MET FDC LINA/MET FDC ALO/MET FDC DPP-4 inhibitors plus MET as individual components
Study Question	What is the cost of EMPA/MET FDC relative to the free-dose combination of its individual components, EMPA and MET, in patients with T2DM?
Type of Economic Evaluation	Cost-minimization analysis
Target Population	Adults with T2DM
Perspective	Canadian public payer
Outcome(s) Considered	Drug costs
Key Data Sources	
Cost	ODB Formulary, including standard markup and dispensing fees, IMS Brogan Delta PA, manufacturer's submitted price
Clinical Efficacy	Bioequivalence studies 1276.5, 1276.6, 1276.7, and 1276.8 comparing FDC with co-administration of EMPA and MET as individual tablets
Harms	
Time Horizon	One year
Results for Base Case	When an 8% markup and an \$8.83 dispensing fee per product every 30 days were included, the manufacturer concluded that EMPA FDC would save between \$109 and \$145 per patient per year, depending on the dose of MET.  When compared with other FDCs of SGLT2 or DPP-4 inhibitors plus MET, and including markup and dispensing fees, the use of EMPA/MET FDC resulted in incremental savings of as much as \$209 and an incremental cost of up to \$63 per patient per year, depending on the comparator.

ALO = alogliptin; CANA = canagliflozin; DAPA = dapagliflozin; DPP-4 = dipeptidyl peptidase-4; EMPA = empagliflozin; FDC = fixed-dose combination; LINA = linagliptin; MET = metformin; ODB = Ontario Drug Benefit; SAXA = saxagliptin; SGLT2 = sodium-glucose cotransporter-2; SITA = sitagliptin; T2DM = type 2 diabetes mellitus.

### Manufacturer's results

The manufacturer presented the annual cost of empagliflozin (EMPA)/metformin (MET) fixed-dose combination (FDC) relative to that of its individual components as the primary analysis, relative to that of other sodium-glucose cotransporter-2 (SGLT2) inhibitor/MET FDCs and free-dose combinations as a secondary analysis, and relative to that of dipeptidyl peptidase-4 (DPP-4) inhibitor/MET FDCs and free-dose combinations as a tertiary analysis. CADTH Common Drug Review (CDR) reviewers regarded these

comparators as appropriate when considering the manufacturer’s reimbursement request to replace individually dosed MET and EMPA in patients already stabilized on the individual components.

The manufacturer reported that the annual cost of EMPA/MET FDC, including an 8% markup and an \$8.83 dispensing fee every 30 days per prescription, is \$1,172 per patient, which is \$110 to \$145 less than that of individually dosed EMPA and MET (\$1,282 to \$1,317 per patient per year). EMPA/MET FDC is also less expensive than other free-dose combinations of an SGLT2 inhibitor and MET (\$1,307 to \$1,330 per patient per year), but \$32 more expensive than dapagliflozin (DAPA)/MET FDC (\$1,140 per patient per year). Canagliflozin (CANA)/MET FDC had been approved in Canada but was not yet marketed at the time of the manufacturer’s analysis; thus, a public price was not yet available for comparison.<sup>7</sup> When compared with combinations of DPP-4 inhibitors plus MET, EMPA/MET FDC is more expensive than saxagliptin (SAXA)/MET FDC and linagliptin (LINA)/MET FDC, but less expensive than sitagliptin (SITA)/MET FDC, alogliptin (ALO)/MET FDC, and all free-dose combinations of a DPP-4 and MET (Table 3).

**TABLE 3: MANUFACTURER’S BASE-CASE RESULTS FOR EMPAGLIFLOZIN/METFORMIN FIXED-DOSE COMBINATION VERSUS OTHER COMBINATIONS OF SODIUM-GLUCOSE COTRANSPORTER-2 OR DIPEPTIDYL PEPTIDASE-4 INHIBITORS PLUS METFORMIN**

Comparator	Strength	Daily Individual Cost (\$)	Daily Drug Cost (\$)	Annual Drug Cost (\$)	Annual Drug Cost (MU + DF, \$)	Incremental Cost (Savings) EMPA/MET FDC (\$)
EMPA/MET FDC (Synjardy)	5 mg/500 mg 5 mg/850 mg 5 mg/1,000 mg 12.5 mg/500 mg 12.5 mg/500 mg 12.5 mg/1,000 mg	1.35 <sup>a</sup>	2.70	986	1,172	NA
<b>Primary comparator — individual component</b>						
EMPA plus MET free-dose combination	10 mg EMPA 1,000 mg MET	2.62 0.09	2.71	988	1,282	(110)
	10 mg EMPA 1,700 mg MET	2.62 0.12	2.74	1,000	1,295	(123)
	10 mg EMPA 2,000 mg MET	2.62 0.18	2.80	1,020	1,317	(145)
	25 mg EMPA 1,000 mg MET	2.62 0.09	2.71	988	1,282	(110)
	25 mg EMPA 1,750 mg MET	2.62 0.12	2.74	1,000	1,295	(123)
	25 mg EMPA 2,000 mg MET	2.62 0.18	2.80	1,020	1,317	(145)
<b>Secondary comparators — other SGLT2/MET FDC and free-dose combinations</b>						
DAPA/MET FDC (Xigduo)	5 mg/850 mg 5 mg/1,000 mg	1.31 <sup>b</sup>	2.62	956	1,140	32
CANA/MET FDC	50 mg/500 mg	NA <sup>c</sup>	NA <sup>c</sup>	NA <sup>c</sup>	NA <sup>c</sup>	NA <sup>c</sup>

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Comparator	Strength	Daily Individual Cost (\$)	Daily Drug Cost (\$)	Annual Drug Cost (\$)	Annual Drug Cost (MU + DF, \$)	Incremental Cost (Savings) EMPA/MET FDC (\$)
(Invokamet)	50 mg/1,000 mg 150 mg/500 mg 150 mg/1,000 mg					
DAPA (Forxiga) plus MET	10 mg + 1,700 mg 10 mg + 2,000 mg	2.74 <sup>b</sup> 2.80	2.77 <sup>d</sup>	1,011	1,307	(135)
CANA (Invokana) plus MET	100 mg + 1,000 mg 100 mg + 2,000 mg 300 mg + 1,000 mg 300 mg + 2,000 mg	2.70 + 0.09 2.70 + 0.18 2.70 + 0.09 2.70 + 0.18	\$2.83 <sup>d</sup>	\$1,033	1,330	(158)
<b>Tertiary comparators — DPP-4 inhibitors/MET FDC and free-dose combinations</b>						
SITA/MET FDC (Janumet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000mg	1.62	3.23	1,180	1,381	(210)
SAXA/MET FDC (Komboglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	1.27	2.54	927	1,109	63
LINA/MET FDC (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	1.3337	2.67	974	1,159	13
ALO/MET FDC (Kazano)	12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg	1.3700 <sup>b</sup>	2.74	1,000	1,188	(16)
SITA (Januvia) plus MET	100 mg + 1,000 mg 100 mg + 1,700 mg 100 mg + 2,000 mg	2.98 + 0.09 2.98 + 0.12 2.98 + 0.18	3.11 <sup>d</sup>	1,120	1,424	(252)
SAXA (Onglyza) plus MET	5 mg + 1,000 mg 5 mg + 1,700 mg 5 mg + 2,000 mg	2.88 + 0.09 2.88 + 0.12 2.88 + 0.18	3.00 <sup>d</sup>	1,097	1,399	(228)
LINA (Trajenta) plus MET	5 mg + 1,000 mg 5 mg + 1,700 mg 5 mg + 2,000 mg	2.55 + 0.09 2.55 + 0.12 2.55 + 0.18	2.68 <sup>d</sup>	978	1,271	(99)

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Comparator	Strength	Daily Individual Cost (\$)	Daily Drug Cost (\$)	Annual Drug Cost (\$)	Annual Drug Cost (MU + DF, \$)	Incremental Cost (Savings) EMPA/MET FDC (\$)
ALO (Nesina) plus MET	25 mg + 1,000 mg 25 mg + 1,700 mg 25 mg + 2,000 mg	2.62 <sup>b</sup> + 0.09 2.62 <sup>b</sup> + 0.12 2.62 <sup>b</sup> + 0.18	2.75 <sup>d</sup>	1,003	1,298	(126)

ALO = alogliptin; CANA = canagliflozin; DAPA = dapagliflozin; DF = dispensing fee; DPP-4 = dipeptidyl peptidase-4; EMPA = empagliflozin; FDC = fixed-dose combination; LINA = linagliptin; MET = metformin; MU = markup; NA = not applicable; SAXA = saxagliptin; SGLT2 = sodium-glucose cotransporter-2; SITA = sitagliptin.

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

<sup>b</sup> Delta PA, manufacturer's list price, accessed July 2016.

<sup>c</sup> A price for CANA/MET FDC was not available at the time of the manufacturer's analysis.

<sup>d</sup> Manufacturer summarized to an average cost using the sum the costs of the included dose combinations divided by the number of combinations.

Source: Adapted from Tables 3 and 4 of manufacturer's pharmacoeconomic (PE) submission. Prices are from Ontario Drug Benefit Formulary (April 2016). Unless otherwise indicated, MET 850 mg tablet is the Saskatchewan Formulary list price (April 2016). Analysis assumed DF of \$8.83 applied every 30 days, and MU of 8%.

The manufacturer conducted a series of one-way sensitivity analyses that increased the number of days per claim from 30 to 90, decreased the patient compliance rate from 100% to 80%, or removed dispensing fees and markups. Increasing the days per claim or eliminating markups and dispensing fees reduced the incremental savings associated with EMPA/MET versus all free-dose combinations. These results are summarized in Table 4.

**TABLE 4: MANUFACTURER'S SENSITIVITY ANALYSES**

Scenario	EMPA/MET FDC Annual Drug Cost (\$)	Comparator Annual Drug Cost (\$)	Incremental Range in Cost (Savings) with EMPA/MET (\$)
Base case • 30 days per claim • 100% compliance • 8% markup and \$8.83 dispensing fees included	1,172	Primary: 1,298 Secondary: 1,140 to 1,330 Tertiary: 1,109 to 1,440	Primary: (126) Secondary: (158) to 32 Tertiary: (268) to 63
90 days per claim	1,100	Primary: 1,155 Secondary: 1,069 to 1,187 Tertiary: 1,037 to 1,310	Primary: (54) Secondary: (87) to 32 Tertiary: (210) to 63
80% compliance	959	Primary: 1,081 Secondary: 934 to 1,107 Tertiary: 908 to 1,162	Primary: (122) Secondary: (148) to 25 Tertiary: (236) to 50
Markup and dispensing fees excluded	986	Primary: 1,003 Secondary: 956 to 1,033 Tertiary: 927 to 1,180	Primary: (17) Secondary: (47) to 29 Tertiary: (194) to 58

EMPA = empagliflozin; FDC = fixed-dose combination; MET = metformin.

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The manufacturer included an average annual cost estimate for each free-dose comparator (e.g., individual DAPA plus MET, individual SITA plus MET), which was the sum of the cost of each dose combination deemed appropriate by the manufacturer and divided by the number of included combinations. This method in effect assumes a uniform patient distribution across included dose combinations, which is unlikely to reflect actual practice. Additionally, the omission of some comparator dosing options (see below) affects this average in some cases. In the absence of data to inform utilization distribution across doses, CDR reanalyses report a range of annual and incremental costs for each comparator combination rather than a single estimate (Table 5).

The manufacturer's analysis did not include the 50 mg/850 mg and 150 mg/850 mg doses of CANA/MET FDC (Invokamet), and this dose combination was also left out of the CANA plus MET free-dose combination. Since the manufacturer conducted its analysis, a wholesale price of \$1.5338 per tablet has become available for CANA/MET FDC (Delta PA, wholesale price, accessed July 2016) and is included in CDR's reanalyses (Table 5).

The manufacturer also included only free-dose combinations with an FDC product containing equivalent doses, rather than all dose combinations within the recommended dose range of the products in question. For example, while DAPA/MET FDC is available only as 5 mg DAPA with 850 mg or 1,000 mg of MET twice daily, the recommended dosing of DAPA as an individual product is 5 mg or 10 mg once daily. This fails to consider that flexibility is an advantage of free-dose combinations when the comparable FDC product has more limited dose options. CDR reanalyses therefore include the 1,000 mg, 1,700 mg, and 2,000 mg daily doses of MET and include all product monograph–recommended daily doses of the DPP-4 inhibitor or SGLT2 inhibitor in question for all free-dose combinations, regardless of whether these doses are available as part of an FDC product (Table 5).

According to CDR's reanalysis of drug costs alone (without dispensing fees or markup), the annual cost of EMPA/MET FDC (\$986 per patient) was \$2 to \$35 less than that of free-dose combinations of EMPA plus MET (\$988 to \$1,020 per patient, depending on the dose of MET). EMPA/MET FDC was also less expensive than CANA/MET FDC (12% less), free-dose combinations of DAPA or CANA plus MET (2% to 6% less), as well as SITA/MET (16% less), and ALO/MET FDC products (1% less), as well as all DPP-4 inhibitor plus MET free-dose combinations (0% to 14% less), with the exception of 5 mg LINA plus 1,000 mg MET daily (2% more). It was more expensive than DAPA/MET (3% more), SAXA/MET (6% more), and LINA/MET (1% more) FDC products. See Table 5 for more detail.

EMPA/MET FDC would also save a dispensing fee per claim over its individual components. The manufacturer assumed a 30-day supply per claim in its base case. However, a larger days' supply is likely appropriate for many patients on stable doses of antidiabetes medications, given the chronic nature of the condition. CDR reviewers therefore recalculated the incremental costs or savings of EMPA/MET FDC versus the various comparators assuming a dispensing fee every 100 days with an 8% markup; EMPA/MET FDC is \$35 to \$70 (3% to 6%) less expensive per patient per year than the Ontario Drug Benefit (ODB) Formulary list prices of its individual components, depending on the dose of MET used.

TABLE 5: CADTH COMMON DRUG REVIEW'S REANALYSIS FOR EMPAGLIFLOZIN/METFORMIN FIXED-DOSE COMBINATION VERSUS OTHER COMBINATIONS OF SGLT2 OR DPP-4 INHIBITORS PLUS METFORMIN

Comparator	Strength	Daily Individual Cost (\$)	Daily Drug Cost (\$)	Annual Drug Cost (\$)	Incremental Cost (Savings) with EMPA/MET FDC (\$)	Annual Drug Cost (MU + DF, \$)	Incremental Cost (Savings) with EMPA/MET FDC (MU + DF, \$)
EMPA/MET FDC (Synjardy)	5 mg/500 mg 5 mg/850 mg 5 mg/1,000 mg 12.5 mg/500 mg 12.5 mg/500 mg 12.5 mg/1,000 mg	1.35 <sup>a</sup>	2.70	986	NA	1,097	NA
<b>Primary comparator — individual components</b>							
EMPA plus MET free-dose combination	10 mg EMPA 1,000 mg MET	2.62 0.09	2.71	988	(2)	1,131	(35)
	10 mg EMPA 1,700 mg MET	2.62 0.12	2.74	1,000	(14)	1,144	(48)
	10 mg EMPA 2,000 mg MET	2.62 0.18	2.80	1,020	(35)	1,166	(70)
	25 mg EMPA 1,000 MET	2.62 0.09	2.71	988	(2)	1,131	(35)
	25 mg EMPA 1,750 mg MET	2.62 0.12	2.74	1,000	(14)	1,144	(48)
	25 mg EMPA 2,000 mg MET	2.62 0.18	2.80	1,020	(35)	1,166	(70)
<b>Secondary comparators — other SGLT2/MET FDC and free-dose combinations</b>							
DAPA/MET FDC (Xigduo)	5 mg/850 mg 5 mg/1,000 mg	1.31 <sup>c</sup>	2.62	956	29	1,140	32
CANA/MET FDC (Invokamet)	50 mg/500 mg 50 mg/850 mg <sup>b</sup> 50 mg/1,000 mg 150 mg/500 mg 150 mg/850 mg <sup>b</sup> 150 mg/1,000 mg	1.53 <sup>c</sup>	3.07	1,120	(135)	1,241	(145)

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Comparator	Strength	Daily Individual Cost (\$)	Daily Drug Cost (\$)	Annual Drug Cost (\$)	Incremental Cost (Savings) with EMPA/MET FDC (\$)	Annual Drug Cost (MU + DF, \$)	Incremental Cost (Savings) with EMPA/MET FDC (MU + DF, \$)
DAPA (Forxiga) plus MET	5 mg + 1,000 mg <sup>b</sup> 5 mg + 1,700 mg <sup>b</sup> 5 mg + 2,000 mg <sup>b</sup> 10 mg + 1,000 mg <sup>b</sup> 10 mg + 1,700 mg 10 mg + 2,000 mg	2.62 <sup>c,d</sup> + 0.09 2.62 <sup>c,d</sup> + 0.12 2.62 <sup>c,d</sup> + 0.18 2.62 + 0.09 2.62 + 0.12 2.62 + 0.18	2.71 to 2.80	989 to 1,021	(3) to (35)	1,132 to 1,167	(35) to (70)
CANA (Invokana) plus MET	100 + 1,000 mg 100 + 1,700 mg <sup>b</sup> 100 + 2000 mg 300 + 1,000 mg 300 + 1,700 mg <sup>b</sup> 300 + 2000 mg	2.70 + 0.09 2.70 + 1.12 2.70 + 0.18 2.70 + 0.09 2.70 + 1.12 2.70 + 0.18	2.78 to 2.87	1,016 to 1,049	(30) to (63)	1,162 to 1,197	(65) to (101)
<b>Tertiary comparators — DPP-4 inhibitors/MET FDC and free-dose combinations</b>							
SITA/MET FDC (Janumet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg	1.62	3.23	1,180	(194)	1,306	(210)
SAXA/MET FDC (Komboglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	1.27	2.54	927	58	1,034	63
LINA/MET FDC (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	1.3337	2.67	974	12	1,084	13
ALO/MET FDC (Kazano)	12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg	1.3700 <sup>c,d</sup>	2.74	1,000	(15)	1,112	(16)
SITA (Januvia) plus MET	100 mg + 1,000 mg 100 mg + 1,700 mg 100 mg + 2,000 mg	2.98 + 0.09 2.98 + 0.12 2.98 + 0.18	3.07 to 3.16	1,120 to 1,152	(135) to (167)	1,274 to 1,309	(177) to (212)
SAXA (Onglyza) plus MET	5 mg + 1,000 mg 5 mg + 1,700 mg 5 mg + 2,000 mg	2.88 + 0.09 2.88 + 0.12 2.88 + 0.18	2.96 to 3.05	1,082 to 1,114	(96) to (129)	1,233 to 1,268	(136) to (171)

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Comparator	Strength	Daily Individual Cost (\$)	Daily Drug Cost (\$)	Annual Drug Cost (\$)	Incremental Cost (Savings) with EMPA/MET FDC (\$)	Annual Drug Cost (MU + DF, \$)	Incremental Cost (Savings) with EMPA/MET FDC (MU + DF, \$)
LINA (Trajenta) plus MET	5 mg + 1,000 mg 5 mg + 1,700 mg 5 mg + 2,000 mg	2.55 + 0.09 2.55 + 0.12 2.55 + 0.18	2.64 to 2.73	963 to 996	22 to (10)	1,105 to 1,140	(8) to (43)
ALO (Nesina) plus MET	25 mg + 1,000 mg 25 mg + 1,700 mg 25 mg + 2,000 mg	2.62 <sup>c,d</sup> + 0.09 2.62 <sup>c,d</sup> + 0.12 2.62 <sup>c,d</sup> + 0.18	2.71 to 2.80	988 to 1,020	(2) to (35)	1,131 to 1,166	(35) to (70)

ALO = alogliptin; CANA = canagliflozin; DAPA = dapagliflozin; DF = dispensing fee; DPP-4 = dipeptidyl peptidase-4; EMPA = empagliflozin; FDC = fixed-dose combination; LINA = linagliptin; MET = metformin; MU = markup; SAXA = saxagliptin; SGLT2 = sodium-glucose cotransporter-2; SITA = sitagliptin.

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

<sup>b</sup> Available combination within the applicable product monograph's recommended dose range but omitted in the manufacturer's analyses.<sup>7-9</sup>

<sup>c</sup> Delta PA, manufacturer's list price, accessed July 2016.

<sup>d</sup> Kazano, Nesina, and Forxiga are reimbursed in Quebec with Régie de l'assurance maladie du Québec (RAMQ) list prices of \$1.1450, \$2.1000, and \$1.4500, respectively.

Source: Prices are from Ontario Drug Benefit Formulary (July 2016) unless otherwise indicated. MET 850 mg tablet is the Saskatchewan Formulary list price (July 2016). Analysis assumed DF of \$8.83 applied every 100 days, and MU of 8%.

## APPENDIX 2: COST TABLE OF OTHER COMPARATORS OF POTENTIAL INTEREST

TABLE 6: COST COMPARISON TABLE FOR NON-INSULIN ANTIDIABETIC DRUGS NOT INCLUDED IN MAIN ANALYSES

Drug/ Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
<i>SGLT2 inhibitors</i>						
Empagliflozin (Jardiance)	10 mg 25 mg	Tab	2.6200	10 mg or 25 mg daily	2.62	956
Canagliflozin (Invokana)	100 mg 300 mg	Tab	2.6960	100 mg or 300 mg daily	2.70	986
Dapagliflozin (Forxiga)	5 mg 10 mg	Tab	2.6200 <sup>a</sup>	5 mg or 10 mg daily	2.62	956
<i>Biguanides</i>						
Metformin	500 mg 850 mg	Tab	0.0444 0.0610 <sup>b</sup>	500 mg three to four times daily	0.18 to 0.23	49 to 65
<i>DPP-4 inhibitors</i>						
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	Tab	2.6177 <sup>a</sup>	25 mg daily	2.62	955
Linagliptin (Trajenta)	5 mg	Tab	2.5500	5 mg daily	2.55	931
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	Tab	2.3997 2.8753	5 mg daily	2.88	1,049
Sitagliptin (Januvia)	25 mg 50 mg 100 mg	Tab	2.9790	100 mg daily	2.98	1,087
<i>GLP-1 receptor analogue</i>						
Dulaglutide (Trulicity)	0.75 mg/0.5 mL 1.5 mg/0.5 mL	4 mL x 0.5 mL pre- filled pen	191.8000 <sup>a</sup>	0.75 mg to 1.5 mg once weekly	6.85	2,493
Exenatide (Bydureon)	2 mg	2 mg pre- filled pen	47.9400 <sup>a</sup>	2 mg once weekly	6.85	2,493
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/mL)	119.7250 <sup>a</sup>	5 mcg to 10 mcg twice daily	3.99	1,457
Liraglutide (Victoza)	2 mL x 3 mL 3 mL x 3 mL	Pre-filled pen (6 mg/mL)	136.98 <sup>b</sup> 205.47 <sup>b</sup>	1.2 mg to 1.8 mg daily	4.57 to 6.85	1,667 to 2,500
<i>Sulfonylureas</i>						

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Drug/ Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Average Daily Drug Cost (\$)	Average Annual Drug Cost (\$)
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 (Diamicon MR)	30 mg 60 mg	ER tab	0.0931 0.2150	30 mg to 120 mg daily	0.09 to 0.43	34 to 157
Glimepiride (generics)	1 mg 2 mg 4 mg	Tab	0.3857 <sup>b</sup>	1 mg to 4 mg daily	0.39	142
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
<i>Thiazolidinediones</i>						
Pioglitazone (generics)	15 mg 30 mg 45 mg	Tab	0.3800 <sup>b</sup> 0.5360 <sup>b</sup> 0.8075 <sup>b</sup>	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 <sup>b</sup> 2.1584 <sup>b</sup> 3.0865 <sup>b</sup>	4 mg to 8 mg daily	2.16 to 3.09	788 to 1,126
Rosiglitazone/ metformin (Avandamet)	2 mg/500 mg 4 mg/500 mg 2 mg/1,000 mg 4 mg/1,000 mg	Tab	1.1959 <sup>b</sup> 1.6424 <sup>b</sup> 1.3062 <sup>b</sup> 1.7857 <sup>b</sup>	4 mg/1,000 mg to 8 mg/2,000 mg daily in divided doses	2.39 to 3.57	873 to 1,304

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

Source: Ontario Drug Benefit Formulary (July 2016) prices unless otherwise indicated.

<sup>a</sup> Delta PA, manufacturer's list price, accessed July 2016.

<sup>b</sup> Saskatchewan Drug Formulary (July 2016).

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