Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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canagliflozin, 100mg and 300mg film-coated tablets (Invokana®)

SMC No. (963/14)

Janssen-Cilag International NV

09 May 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

canagliflozin (Invokana®) is accepted for restricted use within NHS Scotland.

Indication under review: In adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

SMC restriction: to use in the following situations:

- dual therapy in combination with metformin
- triple therapy in combination with metformin plus standard of care
- add-on to insulin therapy in combination with insulin plus standard of care

Treatment with canagliflozin reduces glycosylated haemoglobin (HbA1c) significantly more than placebo when used in combination with various anti-hyperglycaemic regimens (metformin, metformin and sulfonylurea, metformin and pioglitazone, insulin with/without additional anti-hyperglycaemic agents). In addition to metformin, canagliflozin was non-inferior to a sulfonylurea and a dipeptidyl peptidase-4 (DPP-4) inhibitor. In combination with metformin and sulfonylurea, canagliflozin was non-inferior to a DPP-4 inhibitor. Canagliflozin is also associated with reductions in body weight and systolic blood pressure.

Canagliflozin is also licensed for use as monotherapy. The manufacturer's submission related only to the use of canagliflozin as add-on therapy with other glucose-lowering medicinal products. SMC cannot recommend the use of canagliflozin as monotherapy.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Dosing Information

Canagliflozin tablets should be taken orally once a day, preferably before the first meal of the day. Tablets should be swallowed whole. The recommended starting dose is 100mg once daily. In patients tolerating canagliflozin 100mg once daily who have an eGFR ≥60mL/min/1.73m^2 or CrCl ≥60mL/min and need tighter glycaemic control, the dose can be increased to 300mg once daily.

Care should be taken when increasing the dose in patients' ≥75 years of age, patients with known cardiovascular disease, or other patients for whom the initial canagliflozin-induced diuresis poses a risk. In patients with evidence of volume depletion, correcting this condition prior to initiation of canagliflozin is recommended.

When canagliflozin is used as add-on therapy with insulin or an insulin secretagogue (e.g. sulphonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

Product availability date

24 February 2014

Summary of evidence on comparative efficacy

Type 2 diabetes mellitus is a chronic, progressive disease involving insulin resistance, impaired insulin secretion, and increased glucose production. Canagliflozin improves fasting and post-prandial glucose levels by increasing urinary glucose excretion through inhibition of the sodium-glucose co-transporter 2 (SGLT2) mediated reabsorption of glucose from the glomerular filtrate. The degree of anti-hyperglycaemic effect is dependent upon blood glucose levels and glomerular filtration rate. The increase in urinary glucose excretion also produces an osmotic diuresis leading to a reduction in systolic blood pressure and a loss in calories and thus a reduction in body weight.[1] It is the second-in-class to become available in the UK.

The submitting company has requested that SMC considers the use of canagliflozin as:

- Dual therapy in combination with metformin
- Triple therapy in combination with metformin plus standard of care
- Add-on to insulin therapy in combination with insulin plus standard of care.

<u>Dual therapy in combination with metformin</u>

Two similarly designed multicentre, randomised, double-blind, phase III studies (CANTATA-SU and CANTATA-D) recruited adults with type 2 diabetes with inadequate glycaemic control despite treatment with a stable dose of metformin (≥1,500mg/day).[2,3] In CANTATA-SU, HbA1c was required to be between 7% and 9.5%, whereas eligibility for CANTATA-D required HbA1c to be between 7% and 10.5%. Patients taking non-protocol specified doses of metformin and/or taking additional anti-hyperglycaemic therapy were required to meet the HbA1c criteria following

a dose titration/stabilisation phase of 10 to 12 weeks. Patients then entered a two-week placebo run-in.

In CANTATA-SU, patients were randomised 1:1:1 to canagliflozin 100mg (n=483), canagliflozin 300mg (n=485) or glimepiride (n=482, 6mg or 8mg per day) for 52 weeks. In CANTATA-D, patients were randomised 2:2:2:1 to canagliflozin 100mg (n=368), canagliflozin 300mg (n=367), sitagliptin 100mg (n=366) or placebo (n=183) once daily for 26 weeks. Randomisation was stratified by pre-study anti-hyperglycaemic regimen. Glycaemic rescue with pioglitazone (CANTATA-SU) or glimepiride (CANTATA-D) was permitted in both studies. Both studies had double-blind extension phases: in CANTATA-SU, this was a further 52 weeks; in CANTATA-D this was a further 26 weeks, and placebo patients were switched to sitagliptin.

The studies shared a common primary endpoint of change in HbA1c from baseline: to week 52 in CANTATA-SU; and weeks 26 (placebo comparison) and 52 (sitagliptin comparison) in CANTATA-D. Primary analyses were conducted in the modified intention-to-treat (mITT) population, defined as all randomised patients who received at least one dose of study drug, using last observation carried forward (LOCF) to impute missing data. The studies were designed to test non-inferiority between active treatments with a pre-specified margin of 0.3%. CANTATA-D was also designed to test superiority of canagliflozin over placebo. The results of the primary outcomes are presented in Table 1.

Secondary outcomes included changes from baseline in body weight, systolic blood pressure (BP) and the proportions of patients achieving HbA1c <7%. After 52 weeks, canagliflozin 100mg and 300mg were associated with significant reductions in body weight compared with glimepiride (4.4kg and 4.7kg respectively) and sitagliptin (2.1kg and 2.5kg respectively).[3] In CANTATA-SU,[2] the proportions of patients achieving HbA1c <7% after 52 weeks were 54%, 60% and 56% for canagliflozin 100mg, 300mg and glimepiride respectively. In CANTATA-D,[3] the proportions were 41%, 55% and 51% for canagliflozin 100mg, 300mg and sitagliptin respectively. The least squares mean change in systolic blood pressure (95% confidence interval [CI]) was -3.5mmHg (-4.9 to -2.1) for canagliflozin 100mg compared with glimepiride, and -4.8mmHg (-6.2 to -3.4) for 300mg versus glimepiride.[3] In CANTATA-D, differences compared with sitagliptin were -2.9mmHg (-4.5 to -1.3) for canagliflozin 100mg and -4.0mmHg (-5.6 to -2.4) for 300mg.[3]

		Primary Outcome	
		LS mean change in HbA1c from baseline	Between treatment differences, LS mean (95% CI)
CANTATA-SU Outcomes at 52 weeks	Canagliflozin 100mg	-0.82%	vs. glimepiride -0.01% (-0.11 to 0.09)$^{\Delta}$
	Canagliflozin 300mg	-0.93%	vs. glimepiride -0.12% (-0.22 to -0.02) $^{\Delta **}$
	Glimepiride*	-0.81%	-
CANTATA-D Outcomes at 26 / 52 weeks	Canagliflozin 100mg	26 wks: -0.79% 52 wks: -0.73%	vs. placebo -0.62% (-0.76 to -0.48) $^{\#}$ vs. sitagliptin 0% (-0.12 to 0.12) $^{\Delta}$
	Canagliflozin 300mg	26 wks: -0.94% 52 wks: -0.88%	vs. placebo -0.77% (-0.91 to -0.64) $^{\#}$ vs. sitagliptin -0.15% (-0.27 to -0.03) $^{\Delta **}$
	Sitagliptin 100mg	26 wks: -0.82% 52 wks: -0.73%	-
	Placebo	26 wks: -0.17% 52 wks: n/a	-

Table 1: Primary outcomes for studies of canagliflozin in combination with metformin, mITT (LOCF). LS = least squares, CI=confidence interval. *mean maximum dose of glimepiride achieved was 5.6mg/day. [Δ]non-inferiority demonstrated since upper 95% confidence limit is <0.3%. [#] p<0.001. ** superiority demonstrated since upper bound of 95% CI <0.0%.

Triple therapy in combination with metformin plus standard of care

Two studies (CANTATA-D2 and CANTATA-MSU) investigated the addition of canagliflozin to a background of metformin and sulfonylurea.[4,5] The CANTATA-MP study provides evidence of canagliflozin in combination with metformin and pioglitazone.[6,7] These multicentre, randomised, double-blind phase III studies recruited adults with type 2 diabetes with inadequate glycaemic control (HbA1c≥7.0% and ≤10.5%) despite stable metformin (≥1,500mg/day) and sulfonylurea, ≥50% maximal licensed dose (CANTATA-D2 and CANTATA-MSU) or pioglitazone 30mg to 45mg daily (CANTATA-MP). Patients taking non-protocol specified doses of background therapy on screening were eligible if they met the HbA1c criteria following an adjustment period of 8- to 12-weeks duration.

In CANTATA-D2, patients were randomised 1:1 to canagliflozin 300mg (n=378) or sitagliptin 100mg (n=378) daily for 52 weeks. In CANTATA-MSU, patients were randomised 1:1:1 to canagliflozin 100mg (n=157) 300mg (n=156) or matching placebo (n=156) once daily for 26 weeks with an optional 26 week extension period. In CANTATA-MP, patients were randomly assigned 1:1:1 to canagliflozin 100mg (n=113) 300mg (n=114) or placebo (n=115) daily for 26 weeks. In all three studies background antihyperglycaemic therapy was maintained throughout the study. Glycaemic rescue with insulin or glimepiride was permitted in CANTATA-MSU and CANTATA-MP respectively. Patients meeting pre-specified hyperglycaemic criteria in CANTATA-D2 were discontinued from that study.

The primary outcome in all three studies was the change in HbA1c from baseline to week 26 (CANTATA-MSU and CANTATA-MP) or week 52 (CANTATA-D2), conducted in the mITT population using LOCF. CANTATA-D2 was designed to test for non-inferiority of canagliflozin 300mg with sitagliptin at the pre-specified margin of 0.3%. The results of the primary outcomes are presented in Table 2.

		Primary Outcome	
		LS mean change in HbA1c from baseline	Between treatment differences, LS mean (95% CI)
CANTATA-D2	Canagliflozin 300mg	-1.03%	-0.37% (-0.50 to -0.25) [Δ *]
	Sitagliptin 100mg	-0.66%	
CANTATA-MSU	Canagliflozin 100mg	-0.85%	vs. placebo -0.71% (-0.90 to -0.52) [#]
	Canagliflozin 300mg	-1.06%	vs. placebo -0.92% (-1.11 to -0.73) [#]
	Placebo	-0.13%	-
CANTATA-MP	Canagliflozin 100mg	-0.89%	vs. placebo -0.62% (-0.81 to -0.44) [#]
	Canagliflozin 300mg	-1.03%	vs. placebo -0.76% (-0.95 to -0.58) [#]
	Placebo	-0.26%	-

Table 2: Primary outcomes for studies of canagliflozin in combination with metformin plus standard of care (sulfonylurea or pioglitazone), mITT (LOCF). [Δ]non-inferiority demonstrated since upper 95% confidence limit is <0.3%. [#]p<0.001. * superiority demonstrated since upper bound of 95% CI <0.0%.

Secondary outcomes included the change from baseline in body weight, systolic BP and the proportion of patients achieving HbA1c <7%. Canagliflozin 300mg was associated with significant changes in body weight and systolic BP when compared with sitagliptin 100mg:

-2.4kg and -5.9mmHg respectively (p<0.001).[4] No statistical comparison was made between the proportions of patients achieving HbA1c <7%: 48% and 35% respectively. In a separate study, CANTATA-MSU, when added to metformin and sulfonylurea and when compared with placebo at 26 weeks, both doses of canagliflozin were associated with modest but statistically significant reductions in body weight (1.1kg and 1.7kg respectively) and no statistically significant difference in systolic blood pressure.[5] At week 26, the proportions of patients achieving HbA1c <7% were 43%, 57% and 18%, for canagliflozin 100mg, 300mg and placebo respectively.[5]

In CANTATA-MP, when canagliflozin was added to metformin and pioglitazone therapy in comparison with placebo, the results showed: reductions in body weight of 2.5kg to 3.5kg, reduction in systolic blood pressure of 4.1mmHg and 3.5mmHg.[7] Proportions of patients achieving HbA1c <7% were 47%, 64% and 32% for canagliflozin 100mg, 300mg and placebo respectively.[7]

Add-on to insulin therapy in combination with insulin plus standard of care

A pre-specified sub-study of the ongoing CANVAS study provides short-term data for the addition of canagliflozin to an insulin-containing regimen.[8,9,10] The CANVAS study recruited adults with type 2 diabetes with inadequate glycaemic control (HbA1c ≥7% and ≤10.5%) at elevated risk of cardiovascular disease. Elevated risk of cardiovascular disease was defined as either: age ≥30 years with a history of symptomatic atherosclerotic vascular disease; or age ≥50 years with at least two risk factors for vascular disease. The insulin sub-study included patients recruited to CANVAS who were taking insulin (≥30units/day) with or without additional anti-hyperglycaemic agents at study outset. Background therapy was required to have been stable in the previous eight weeks.

Patients were randomised 1:1:1, to canagliflozin 100mg, 300mg and placebo once daily, with stratification for baseline use of background anti-hyperglycaemic therapy. Background anti-hyperglycaemic therapy was to be maintained at stable doses for the duration of sub-study with fasting plasma glucose levels (FPG) guiding the requirement for glycaemic rescue.

The primary outcome of the sub-study was the change in HbA1c from baseline to week 18 conducted in the mITT population and using LOCF. At week 18, the least squares mean change in HbA1c from baseline was -0.63%, -0.72% and 0.01% for canagliflozin 100mg (n=566), canagliflozin 300mg (n=587) and placebo (n=565) respectively. Placebo-subtracted differences in least squares mean changes were -0.65% (p<0.001) for canagliflozin 100mg, and -0.73% (p<0.001) for canagliflozin 300mg.

Results of relevant secondary endpoints were statistically significant in favour of both doses of canagliflozin. The proportions of patients achieving HbA1c <7% were 20%, 25% and 7.7% for canagliflozin 100mg, 300mg and placebo respectively.[9] The placebo-adjusted least-squares mean changes in body weight were -1.8kg for canagliflozin 100mg and -2.3kg for 300mg. Systolic blood pressure was reduced by 5.1mmHg, 6.9mmHg and 2.5mmHg in the canagliflozin 100mg, 300mg and placebo groups respectively.[9]

Summary of evidence on comparative safety

Across the six phase III studies, similar proportions of patients in the canagliflozin treatment groups reported adverse events (range 63% to 77% for canagliflozin 300mg and 59% to 72% for canagliflozin 100mg). There were low rates of discontinuation due to adverse events, ranging in the canagliflozin groups from 2% to 8%.

The proportion of patients experiencing hypoglycaemic episodes was low except when canagliflozin was added to sulfonylurea-, or insulin-based background anti-hyperglycaemic regimens. In combination with metformin in CANTATA-SU, 5% to 6% of canagliflozin patients reported hypoglycaemia compared with 34% of glimepiride patients. In CANTATA-D, the proportions of patients in the canagliflozin and sitagliptin groups that had hypoglycaemic episodes were 6.8% versus 4.1% respectively.[2,3] In combination with metformin and sulfonylurea; the proportions were 43% for canagliflozin 300mg and 41% for sitagliptin; a greater proportion of canagliflozin patients reported hypoglycaemia compared with placebo (34% to 36% versus 18%).[4,5] In combination with metformin and pioglitazone, the proportions reporting hypoglycaemia were 2.7% to 5.3% in the canagliflozin groups compared with 2.6% in the placebo group.[7] When commenced on a background of insulin, hypoglycaemia was reported in 49% of canagliflozin patients compared with 37% of placebo patients.[9]

Adverse events predicted by canagliflozin's mechanism of action were more common in canagliflozin patients compared with control: these included genital mycotic infection, urinary tract infection, and adverse events related to osmotic diuresis.

As part of the Registration process, a meta-analysis of phase II and III studies was conducted to define the risk of cardiovascular events with canagliflozin. The meta-analysis included 9,632 patients and 10,383 total patient-years of exposure (6,888 years with canagliflozin and 3,495 years for control). No excess risk of major adverse cardiovascular events was suggested. The hazard ratio for canagliflozin compared with control was 0.98 (95% CI: 0.70 to 1.37).[10]

Summary of clinical effectiveness issues

Canagliflozin is the second SGLT-2 inhibitor to be marketed in the UK. As per UK guidelines and existing SMC advice,[11,12] a broad range of anti-diabetic therapies are considered relevant comparators for the indications for which the company wishes canagliflozin to be considered (Table 3).

Indication under consideration	Comparator class
Dual therapy with metformin	sulfonylureas, pioglitazone, DPP-4 inhibitors, Glucagon-like peptide-1 (GLP-1) agonists, dapagliflozin
Triple therapy (metformin & sulfonylurea)	pioglitazone, DPP-4 inhibitors, GLP-1 agonists, insulin
Triple therapy (metformin & pioglitazone)	DPP-4 inhibitors, GLP-1 agonists, insulin
Add-on to insulin	pioglitazone, DPP-4 inhibitors, GLP-1 agonists, prandial insulin

Table 3: Relevant comparator classes for each indication under review by SMC.

The results of the six pivotal phase III studies demonstrated that addition of canagliflozin (100mg or 300mg daily) to existing anti-hyperglycaemic therapy is associated with clinically significant improvements in glycaemic control, as measured by reductions in HbA1c, when compared with placebo. When used as dual therapy in combination with metformin, canagliflozin was non-inferior to glimepiride and sitagliptin. Although the 300mg dose of canagliflozin was statistically superior to the active comparators, the treatment differences were not clinically significant (Table 1). However, when added to metformin and sulfonylurea treatment, a potentially clinically significant difference in favour of canagliflozin 300mg was found compared with sitagliptin (Table 2).

All six studies evaluated change in HbA1c as the primary outcome. This is a validated outcome in studies in type 2 diabetes, since reduction in HbA1c is associated with a reduction in microvascular and macrovascular complications. Treatment guidelines recommend HbA1c targets in the treatment of diabetes.[11,12] The way in which HbA1c results are expressed in the UK has changed; results are now reported as mmol/mol rather than as a percentage. The equivalent of the HbA1c targets of 6.5% and 7.0% are 48mmol/mol and 53mmol/mol in the new units.

Direct comparative data are only available for canagliflozin versus a sulfonylurea or a DPP-4 inhibitor. To support the economic case, which compared canagliflozin against a range of treatment options, the company presented four network meta-analyses (NMA) of anti-hyperglycaemic agents in combination with: metformin (17 studies), metformin and sulfonylurea (9 studies), metformin and pioglitazone (2 studies), and as an add-on to insulin (14 studies). The NMA focused upon key agents within each therapeutic class, selected on the basis of market share and/or SMC status: gliclazide, pioglitazone, sitagliptin, exenatide, and dapagliflozin. Insulins were included in the networks, but it was not possible to include neutral protamine Hagedorn or prandial insulins. Several outcomes were compared: the change from baseline in HbA1c, body weight, body-mass index (BMI), systolic blood pressure (BP) and the risk of hypoglycaemic events, all measured after 26 weeks of treatment except in the dual therapy network (at 52 weeks). Comparisons of hypoglycaemic events were confounded by differing definitions of hypoglycaemia between the constituent studies in the networks, so are not discussed further.

Dual therapy in combination with metformin NMA

Canagliflozin was compared with gliclazide, pioglitazone, exenatide, sitagliptin and dapagliflozin. Heterogeneity between the constituent studies was identified which may have confounded the comparisons (particularly the HbA1c outcome) for or against canagliflozin. The results should be interpreted with caution. No evidence of a difference between treatments was identified for change in HbA1c from baseline. Both doses of canagliflozin were associated with similar changes in body weight compared with exenatide and dapagliflozin, and greater reductions when compared with gliclazide, pioglitazone and sitagliptin. There was no evidence of a difference between the treatments for change in BMI. Canagliflozin was associated with reductions in systolic BP compared with sitagliptin, and in comparison with pioglitazone the treatment difference was dose dependant.

Triple therapy (in combination with metformin and sulfonylurea) NMA

Canagliflozin was compared with sitagliptin and exenatide. Canagliflozin was associated with similar changes in HbA1c and body weight compared with sitagliptin and exenatide. A comparison with sitagliptin could only be made for change in BMI and systolic BP, and there was evidence to suggest that canagliflozin was superior for these outcomes. A sensitivity analysis in which an Asian sub-group was excluded suggested that canagliflozin was associated with weight reduction compared with sitagliptin and exenatide.

Triple therapy (in combination with metformin and pioglitazone) NMA

Canagliflozin was compared with sitagliptin. Only changes in HbA1c and body weight could be compared and no evidence of a difference between canagliflozin and sitagliptin was identified in the analysis.

Add-on to insulin-containing regimen NMA

Canagliflozin was compared with pioglitazone, exenatide, sitagliptin and dapagliflozin. Significant heterogeneity between the studies was identified such as variations in: patient populations' duration of diabetes, baseline HbA1c, baseline dose and subsequent on-study

titration of background insulin. These confounding factors are limitations to the analysis. The NMA results suggested no difference between the treatments for the change in HbA1c and variable comparative changes in body weight. Comparison with dapagliflozin and exenatide was only possible for the change in systolic BP and no evidence of a difference was identified.

In general, clinical experts consulted by SMC considered canagliflozin to be an alternative to dapagliflozin. SMC has previously restricted dapagliflozin to use as dual therapy with metformin, where a sulphonylurea is inappropriate, and more recently to use as add-on therapy to insulin.

The efficacy of SGLT-2 inhibitors is reliant upon renal function. A potential advantage of canagliflozin is that it can be continued at a dose of 100mg in patients whose renal function has deteriorated below an estimated glomerular filtration rate (eGFR) of 60mL/min/1.73m^2 or creatinine clearance (CrCl) <60mL/min,[1] although it should be discontinued when eGFR is below 45mL/min/1.73m^2 or CrCl <45 mL/min. The alternative SGLT-2 inhibitor, dapagliflozin, is not recommended when eGFR is below 60mL/min/1.73m^2.[14]

Summary of comparative health economic evidence

The economic evaluation submitted by the company for type 2 diabetes mellitus patients consisted of a number of cost utility analyses that were carried out to compare canagliflozin (100mg and 300mg doses) with the following treatment options depending on the line of treatment:

- For dual therapy in combination with metformin, canagliflozin was compared to thiazolidinediones (TZD [pioglitazone]), sulphonylureas, DPP-4 inhibitors (sitagliptin), dapagliflozin and GLP-1 agonists (exenatide).
- For triple therapy (metformin+sulphonylurea and metformin+TZD), canagliflozin was compared to the DPP-4 inhibitors, the GLP-1 agonists (exenatide) (only in the metformin+sulphonylurea analysis) and long acting insulin (only in the metformin+sulphonylurea analysis).
- For the add-on to insulin therapy, the comparators were the DPP-4 inhibitors (sitagliptin) and the GLP-1agonists (exenatide).

The comparators were deemed broadly appropriate. However, based on SMC clinical expert responses and previous SMC decisions, the following comparators were deemed to be most relevant: dapagliflozin for dual therapy, DPP-4 inhibitors (sitagliptin) for triple therapy, and GLP-1 agonists (exenatide) for add-on to insulin therapy.

The company used a micro simulation model with a 40 year time horizon and cycle length of one year. Cohorts of patients moved through the model based on a set of characteristics, and would move into health states designed to reflect the natural progression of type 2 diabetes mellitus. The health states included: complication free, chronic kidney disease, neuropathy, retinopathy, and a variety of macro-vascular events (such as stroke, myocardial infarction, and congestive heart failure). All analyses were carried out from an NHS Scotland perspective.

The key clinical evidence relating to the relative treatment effects came from the NMAs described above. These analyses were conducted around the following outcome measures: HbA1c, systolic blood pressure, weight/BMI, and incidence of hypoglycaemic events. The utility values in the base case were primarily derived from a separate published study (chosen following a systematic review), appropriate literature and assumptions. Adverse event disutilities were also taken into account and, when not available, were derived from a time trade-off (TTO) utility study.

Regarding cost data, all relevant medicine costs were included in each analysis, although the cost of metformin was not included as this was assumed to be equal across treatment arms. No administration costs were included, and no renal or liver function monitoring tests were taken into account since these tests are part of routine clinical monitoring for this patient group. Adverse event costs were included, for example for the treatment of genital mycotic infections and urinary tract infections.

The base case results are presented in the following tables. Although the results of a number of analyses are presented, the key results for consideration are those for the most relevant comparators identified above.

Dual therapy

Table 1: Base case results for canagliflozin (both doses) in dual therapy.

Comparator	Incremental costs	Incremental QALYs	ICER
Canagliflozin 100mg			
TZD	£1,334	-0.142	Dominated
Sulphonylurea	£319	0.136	£2,353
DPP-4-inhibitors	£72	0.007	£9,676
Dapagliflozin	£138	0.017	£8,220
GLP-1-agonists	-£628	-0.008	£77,706[#]
Canagliflozin 300mg			
TZD	£1,687	-0.129	Dominated
Sulphonylurea	£769	0.137	£5,600
DPP-4-inhibitors	£423	0.016	£26,875
Dapagliflozin	£434	0.022	£19,624
GLP-1-agonists	-£246	-0.001	£229,381[#]

canagliflozin is both cheaper and less effective than GLP-1-a, therefore ICER is for GLP to replace canagliflozin 100mg. ICER – incremental cost-effectiveness ratio, QALY – quality adjusted life years

Triple therapy

Table 2: Base case results for canagliflozin (both doses) in triple therapy (without TZD).

Comparator	Incremental costs	Incremental QALYs	ICER
Canagliflozin 100mg			
DPP-4-inhibitors	£45	0.021	£2,158
GLP-1-agonists	-£721	0.002	Dominant
Insulin	£380	0.195	£1,951
Canagliflozin 300mg			
DPP-4-inhibitors	£426	0.019	£22,187
GLP-1-agonists	-£256	0.004	Dominant
Insulin	£704	0.276	£2,555

Add-on to insulin therapy

Table 3: Base case incremental cost-effectiveness results for canagliflozin 100mg in add-on to insulin therapy.

Comparator	Incremental costs	Incremental QALYs	ICER
Canagliflozin 100mg			
DPP-4-inhibitors	£69	-0.003	Dominated
GLP-1-agonists	-£391	-0.044	£8,879[#]

Canagliflozin 300mg			
DPP-4-inhibitors	£200	0.032	£6,250
GLP-1-agonists	-£194	-0.001	£132,540[#]

canagliflozin is both cheaper and less effective than GLP-1-a, therefore ICER is for GLP to replace canagliflozin 100mg. ICER – incremental cost-effectiveness ratio, QALY – quality adjusted life years

The key uncertainty associated with the analyses stems from the NMAs that are used to estimate the respective treatment effects of the medicines. There was some concern from the New Drugs Committee that the treatment effects may be overestimated in the economic model as for some parameters no evidence of differences were identified. In response to this, the submitting company provided some more conservative analyses in which any differences in treatment effect that were small relative to their variability were excluded. These analyses showed some uncertainty in the results, particularly for the 100mg analyses versus dapagliflozin where differences in costs and outcomes were very small.

Other uncertainties associated with the analysis are as follows;

- The company has included a metabolic drift assumption within their analysis where, over time and regardless of treatment, biomarkers such as HbA1c 'drift' up. The inclusion of this drift assumption may be appropriate, yet there is some concern that the company has assumed that the drift occurs over a longer term than is appropriate. However, for the key comparators, the drift assumption was the same for canagliflozin and the comparator treatments, which lessened the concern about this assumption.

- As with other SMC submissions using diabetes models, there was some concern surrounding the appropriateness of using short term outcome measures to estimate long term treatment effects. However, the company has developed their economic analysis taking account of relevant good practice guidance for economic modelling.

Despite these limitations and uncertainties, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Information Group.

- A submission was received from Diabetes UK Scotland, a UK registered charity.

- Diabetes UK Scotland has received funding from several pharmaceutical companies in the past 2 years.

- Diabetes UK Scotland highlights the growing incidence of diabetes which currently affects over 250,000 people in Scotland. This complex condition accounts for approximately 10% of NHS Scotland spending (~£1bn per year) of which 80% is spent on largely avoidable complications of poorly controlled diabetes, including blindness, amputations, renal disease, coronary heart disease and stroke.

- Patients highlight "the balancing act of managing diabetes is overwhelming". They frequently struggle with weight gain caused by medication and there can be a financial impact of reduced working or loss of employment.

- Depression is an important co-morbidity due to the severe impact on quality of life. Research has indicated that life expectancy in Type 2 diabetes can be reduced by approximately 14 years.

- Advantages of canagliflozin are a once daily oral regime with a new mode of action, and potentially less gastric disturbance, reduced risk of hypoglycaemia, improved blood pressure control, less weight gain and reduced micro and macro-vascular complications.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published updated guidance on the "Management of diabetes" in March 2010.[11] The guideline recommends that treatment targets should be individualised to balance the harms of hypoglycaemia and weight gain with the benefits in reducing the risk of microvascular and macrovascular disease. Target glycosylated haemoglobin (HbA1c) of 7.0% (53mmol/mol) is reasonable in people with type 2 diabetes mellitus, and in newly diagnosed patients, this target may be intensified to 6.5% (48mmol/mol). The treatment algorithm notes several options for second and third-line treatment of type 2 diabetes mellitus to be added in combination with metformin and/or sulfonylurea; additional oral anti-diabetic drugs, pioglitazone or DPP-4 inhibitors; or injections of GLP-1 analogues or commencement of insulin. Treatment should be continued if an individualised target is reached or the HbA1c falls at least 0.5% in 3 to 6 months. With respect to using insulin in patients with type 2 diabetes, oral sulphonylurea and metformin therapy should be continued when insulin is initiated to maintain or improve glycaemic control. Once daily, neutral protamine Hagedorn insulin is the first choice of insulin to be used, but basal insulin analogues can be considered if there are concerns regarding the risk of hypoglycaemia. The bedtime basal insulin should be titrated against the morning or fasting glucose and if HbA1c targets are not reached then the addition of prandial insulin should be considered.

The National Institute for Health and Care Excellence published NICE Clinical Guideline 87 – Type 2 diabetes - newer agents, in May 2009.[12] The guideline considered sulfonylurea, DPP-4 inhibitors or pioglitazone as suitable second-line options to be used in combination with metformin and advised on cost effective use of exenatide as a third-line agent. The guideline recommended that patients using basal insulin regimens (e.g. neutral protamine Hagedorn or long-acting analogues) be monitored for the need to increase the dose and/or intensify the regimen using short-acting insulin before meals, or pre-mixed insulin. Patients using pre-mixed insulin should be monitored to determine if they need further injections of short-acting insulin before meals or conversion to a basal-bolus regimen. Combination of pioglitazone and insulin was considered appropriate for patients; who have inadequate glycaemic control despite high-dose insulin therapy; or who have had a significant response to thiazolidinedione therapy in the past.

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) published a position statement "Management of Hyperglycaemia in type 2 diabetes: a patient-centred approach" in June 2012.[13] A patient-centred approach is advocated with individualisation of treatment. Beyond lifestyle advice and initial drug therapy with metformin a number of treatment options are recommended with no specific preference: choice is based on patient and drug characteristics.

Additional information: comparators

In addition to diet and exercise, pharmacological approaches to manage hyperglycaemia that could be used for the indications reviewed in this submission include: sulfonylureas, pioglitazone, dipeptidyl-peptidase IV inhibitors, glucagon-like peptide 1 agonists, insulin and the other SGLT-2 inhibitor (dapagliflozin).

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Canagliflozin	**100mg or 300mg orally once daily**	**476 to 607**
Liraglutide	Maintenance dose of 1.2 to 1.8mg once daily by subcutaneous injection	952 to 1,428
Exenatide	5 to 10micrograms twice daily by subcutaneous injection	828
Lixisenatide	Maintenance dose of 20micrograms once daily by subcutaneous injection.	657
Dapagliflozin	10mg orally once daily	476
Linagliptin	5mg orally once daily	432
Sitagliptin	100mg orally once daily	432
Vildagliptin	50mg orally twice daily	413
Saxagliptin	5mg orally once daily	411
Pioglitazone	15 to 45mg orally once daily	54 to 84
Gliclazide	40 to 320mg orally in one or two divided doses	44 to 53
Glimepiride	1 to 6mg orally once daily	14 to 32

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 03 March 2014, except canagliflozin from company's submission. Not all sulfonylureas are represented and insulins not tabled.

Additional information: budget impact

For dual therapy:
The submitting company estimated the population eligible for treatment to be 36 in year 1 and 1660 in year 5, with an estimated uptake rate of 0.09% in year 1 and 3.49% in year 5. The gross impact on the medicines budget was estimated to be £17k in year 1 and £814k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact is estimated to be £12k in year 1 and £264k in year 5.

For triple therapy:
The submitting company estimated the population eligible for treatment to be 184 in year 1 and 2,644 in year 5, with an estimated uptake rate of 1.22% in year 1 and 14.57% in year 5. The gross impact on the medicines budget was estimated to be £90k in year 1 and £1.29m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact is estimated to be £70k in year 1 and £606k in year 5.

Add-on to insulin:
The submitting company estimated the population eligible for treatment to be 73 in year 1 and 913 in year 5, with an estimated uptake rate of 0.2% in year 1 and 2.1% in year 5. The gross impact on the medicines budget was estimated to be £36k in year 1 and £448k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact is estimated to be £31k in year 1 and £335k in year 5.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

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12) National Institute for Health and Care Excellence. Type 2 diabetes: management of type 2 diabetes (clinical guideline 87), 2009. www.nice.org.uk
13) Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycaemia in type 2 diabetes: a patient-centred approach. Diabetes Care 2012; 35:1364-79.
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This assessment is based on data submitted by the applicant company up to and including 14 April 2014.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and

NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.