



dapagliflozin 5mg film coated tablets (Forxiga®)

AstraZeneca UK Ltd

9 August 2019

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

dapagliflozin (Forxiga®) is accepted for use within NHSScotland.

Indication under review: In adults for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI $\geq 27\text{kg/m}^2$, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

Dapagliflozin in combination with insulin improved glycaemic control compared with insulin alone in adult patients with inadequately controlled type 1 diabetes.

Chairman
Scottish Medicines Consortium

Indication

Dapagliflozin is indicated in adults for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI $\geq 27\text{kg/m}^2$, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.¹

Dosing Information

The recommended dose is 5mg once daily. Dapagliflozin can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

When used for type 1 diabetes mellitus, dapagliflozin must only be administered as an adjunct to insulin.

To minimise the risk of diabetic ketoacidosis, treatment with dapagliflozin should be initiated and supervised by specialists in type 1 diabetes. See the Summary of Product Characteristics (SPC) for further details including details on ketone monitoring.¹

Product availability date

5 April 2019

Summary of evidence on comparative efficacy

Dapagliflozin is an inhibitor of sodium-glucose co-transporter 2 (SGLT2). It lowers blood glucose levels, independently of insulin, by reducing renal glucose reabsorption leading to increased urinary glucose excretion. The magnitude of urinary glucose excretion is affected by the blood glucose concentration and renal function.¹ Dapagliflozin is currently available for the treatment of patients with type 2 diabetes and is the first licensed adjunct to insulin for the treatment of insufficiently controlled type 1 diabetes.

The evidence to support the efficacy and safety of dapagliflozin in patients with type 1 diabetes comes from the DEPICT-1 and DEPICT-2 studies, both multicentre, randomised, double-blind, placebo-controlled, phase III studies.²⁻⁴ Both studies had a similar design which included an 8-week lead-in period to assess and optimise glycaemic control, a 24-week double-blind short-term treatment period, a 28-week patient and site blinded long-term treatment period, and a 4-week follow-up period.²⁻⁴ The studies recruited patients with type 1 diabetes aged 18 to 75 years, with inadequate glycaemic control despite at least one year of ongoing insulin treatment. Patients' total insulin dose was required to be ≥ 0.3 international units/kg/day for ≥ 3 months before screening. Patients were required to have glycated haemoglobin (HbA1c) levels of $\geq 7.5\%$ to $\leq 10.5\%$ (58.5 to 91.3 mmol/mol) and a BMI of $\geq 18.5\text{kg/m}^2$ at randomisation.²⁻⁴

Patients were randomised equally to either dapagliflozin 5mg, dapagliflozin 10mg or placebo, all taken orally once daily and as an adjunct to continuing adjustable insulin therapy. The

dapagliflozin 10mg dose has not been licensed for the indication under review and will not be discussed further. It was recommended that study patients' daily insulin dose was reduced by up to 20% following administration of the first dose of the study medicine to reduce the risk of hypoglycaemia. The timing and degree of reductions in insulin dose were at the investigators' discretion. Insulin doses could then be titrated back towards baseline level if appropriate. The study protocol did not specify standardised insulin titration algorithms.²⁻⁴ Randomisation was stratified by current use of continuous glucose monitoring (yes or no), method of insulin administration (multiple daily injections [MDI] or continuous subcutaneous insulin infusion [CSII]), and baseline HbA1c (≥ 7.5 to $< 9\%$ or ≥ 9 to $\leq 10.5\%$).²⁻⁴

The primary efficacy outcome was the change from baseline in HbA1c at week 24 in the dapagliflozin groups compared with the placebo group. In both studies the primary efficacy analyses were conducted in the full analysis set which included all patients who had taken at least one dose of study medicine during the 24-week treatment period.²⁻⁴ The primary analysis was a longitudinal repeated measures analysis which assumed that missing data was missing at random.

The results of both studies indicated superiority of dapagliflozin 5mg over placebo, both in combination with adjustable insulin, for the primary outcome of adjusted mean change in HbA1c from baseline to week 24. The results are detailed in Table 1.

Table 1. Primary outcome results of the DEPICT-1 and DEPICT-2 studies at week 24.⁴

	DEPICT-1		DEPICT-2	
	Dapagliflozin 5mg (n=259)	Placebo (n=260)	Dapagliflozin 5mg (n=271)	Placebo (n=272)
Baseline mean HbA1c (%)	8.52	8.50	8.45	8.40
Adjusted mean change from baseline % (95% CI)	-0.45 (-0.55 to -0.34)	-0.03 (-0.13 to 0.08)	-0.34 (-0.43 to -0.25)	0.03 (-0.06 to 0.12)

CI = confidence interval, HbA1c = glycated haemoglobin. All treatments were in combination with adjustable insulin

Most of the reduction in HbA1c for patients treated with dapagliflozin was observed during the first 4 weeks of treatment, and was sustained to week 24.⁴ In a subgroup analysis of pooled study data, the effect of dapagliflozin 5mg compared with placebo for change in HbA1c from baseline to week 24 was consistent with the primary analysis across all subgroups tested. For the subgroups of patients with BMI > 27 to $\leq 30\text{kg/m}^2$ and $> 30\text{kg/m}^2$ respectively (i.e. the licenced population), comparisons of dapagliflozin 5mg with placebo resulted in differences in HbA1c change from baseline of -0.41% and -0.44%. The studies were not powered for the comparison of dapagliflozin 5mg with placebo for these subgroups of patients.⁴

A sequential testing procedure allowed for the formal testing of key secondary outcomes included in the hierarchy. Dapagliflozin demonstrated statistically significant advantages over placebo for all key secondary outcomes. The details of selected secondary outcomes are included in Table 2. The results indicate greater weight loss, greater insulin dose reduction, a decrease in blood glucose variability, and a greater response rate ($\geq 0.5\%$ reduction in HbA1c without a severe hypoglycaemic event) associated with dapagliflozin treatment compared with the placebo group.⁴

Table 2. Selected secondary outcome results from the DEPICT-1 and DEPICT-2 studies.⁴

	DEPICT-1		DEPICT-2	
Change from baseline to week 24 in:	Dapagliflozin 5mg (n=259)	Placebo (n=260)	Dapagliflozin 5mg (n=271)	Placebo (n=272)
Adjusted mean total daily insulin dose, %	-7.74	1.16	-8.73	2.29
Bodyweight, adjusted mean % change	-3.00	0.05	-3.22	-0.02
Mean amplitude of glucose excursion (MAGE) of the 24-hour glucose readings, mg/dL	-14.9	2.4	-10.2	-0.3
Proportion with a reduction of HbA1c of $\geq 0.5\%$ without a severe hypoglycaemic event	50%	25%	40%	20%

For the secondary outcome, change from baseline in mean continuous glucose monitoring readings at week 24, statistically significant reductions were demonstrated for dapagliflozin compared with placebo in both studies.²⁻⁴

Longer term outcomes

For both studies, exploratory efficacy analyses were conducted at week 52, the end of the 28-week long-term extension period. The results indicate a continued dapagliflozin 5mg treatment effect for the efficacy outcomes and a sustained advantage over placebo. There was a reduction in the magnitude of the HbA1c change from baseline at 52 weeks compared with at 24 weeks:

DEPICT-1

-0.45% at 24 weeks compared with -0.27% at 52 weeks and DEPICT-2 -0.34% at 24 weeks compared with -0.11% at 52 weeks. The reduction in bodyweight from baseline for patients treated with dapagliflozin 5mg compared with patients treated with placebo was maintained from week 24 to week 52.⁴

Indirect evidence

In the absence of direct data comparing dapagliflozin plus adjustable insulin with off-label metformin plus adjustable insulin, the submitting company presented Bayesian Network Meta-Analyses (NMAs) to indirectly compare these treatments, in adult patients with type 1 diabetes, for the following outcomes: change in HbA1c from baseline, change in bodyweight from baseline

(both to week 24 and week 52); change in insulin dose, incidence of hypoglycaemia adverse events and hypoglycaemia serious adverse events (all at week 52 only). The evidence to support dapagliflozin was taken from the DEPICT studies and the evidence to support metformin came from Lund 2008 and REMOVAL studies.^{5, 6} The results indicate dapagliflozin plus insulin is likely to provide greater improvements in HbA1c and weight reduction compared with metformin plus insulin following 24 weeks and 52 weeks of treatment. Credible intervals were very wide for the other outcomes compared, and no conclusions can be drawn from these comparisons.

Summary of evidence on comparative safety

The safety profile of dapagliflozin in the type 1 diabetes population is similar to the type 2 diabetes population with the exception of increased risk of diabetic ketoacidosis (DKA) which is a potentially life-threatening complication.⁴

Safety analyses were based on the safety analysis set, which included all randomised patients who had received one dose of study medicine, and the results reported are for the pooled DEPICT-1 and DEPICT-2 studies from the 24-week short-term treatment period. The adverse event (AE) analyses of the short-term plus long-term treatment periods of the DEPICT-1 study were consistent with the analysis of the short-term period alone.⁴

In the pooled 52-week data, events adjudicated as 'definite' DKA were reported in 4.0% patients in the dapagliflozin 5mg and 1.1% patients in the placebo group. Inadequate insulin doses were the most common precipitating factor.⁴ Because of this increased risk the European Medicines Agency (EMA) limited the licensed population to overweight or obese patients with a BMI $\geq 27\text{kg/m}^2$. In addition, the SPC recommends that dapagliflozin is not used in patients with low insulin need.¹

For the 24-week short term treatment period, the following were reported for the pooled dapagliflozin 5mg plus insulin group (n=548) and the placebo plus insulin group (n=532) respectively: patients with at least one AE 70% and 62%, treatment-related AEs 29% and 12%, treatment-related serious AEs 3.3% and 0.6%, and AEs leading to discontinuation of study medicine 4.2% and 3.8%, viral upper respiratory tract infections 14% and 15%, genital infections 11% and 2.3%, urinary tract infections 6.8% and 4.7% , upper respiratory tract infection 5.7% and 4.3%, pollakiuria (extraordinary daytime urinary frequency) 5.7% and 2.6%. The following AEs of interest were reported for the same groups: hypersensitivity reactions 5.5% and 3.6%, 'definite' DKA 2.0% and 0.6%, fractures 1.5% and 0.9%, severe hypoglycaemia 1.0% and 1.2%, renal impairment 1.1% and 0.0% and cardiovascular events 0.4% and 0.4%.⁴

Most AEs reported in the 24-week pooled analysis were of mild intensity. Most of the differences observed in the AE profiles of the dapagliflozin and placebo groups can be attributed to events associated with genital infections and increased urinary frequency/output, which are well known AEs of dapagliflozin.⁴

Summary of clinical effectiveness issues

Type 1 diabetes is an autoimmune disorder which results in chronic hyperglycaemia from the destruction of insulin producing cells. Macrovascular and microvascular diabetes-related complications and glycaemic variability negatively impact on patients' quality of life and length of life. Treatment for type 1 diabetes is lifelong replacement insulin. However, many patients are unable to achieve glycaemic control. The optimisation of insulin dosing is challenging, and many patients suffer harmful episodes of insulin-related hypoglycaemia and DKA (reported in 5 to 7% of patients with type 1 diabetes), associated with suboptimal insulin dosing. These episodes impact on patient psychology and quality of life through anxiety about insulin dosing and the harmful physical effects.⁴ Increasing insulin doses are associated with weight gain. Dapagliflozin is the first licensed insulin-adjunct treatment for patients with type 1 diabetes; off-label metformin may sometimes be used at present, based on limited evidence.⁴

The results of both DEPICT studies were consistent; following 24 weeks of treatment, addition of dapagliflozin to adjustable insulin was associated with a reduction in HbA1c compared with placebo. This reduction was achieved in combination with reductions in insulin requirements and in bodyweight. HbA1c is an established measure of glucose control over the preceding two to three months and has been shown to be associated with the risk of developing diabetic microvascular complications.⁷

The reduction in HbA1c associated with dapagliflozin at 24 weeks was considered to be modest by the EMA and the majority of experts consulted by the European organisation considered the reduction to be of 'borderline' clinical relevance.⁴

The licensed population represented just over half of the overall trial population and the study was not powered for the subgroup of interest, patients with BMI $\geq 27\text{kg/m}^2$, although treatment effect was consistent across all subgroups analysed.⁴ The exclusion of patients with common diabetic co-morbidities such as mild to moderate renal impairment, recent cardiovascular disease, or unstable glycaemic control means there is some uncertainty regarding the generalisability of the studies' results to the Scottish population.

The risk of potentially life-threatening DKA versus the benefit of improved glycaemic control and weight reduction was considered by the EMA to be acceptable in the subgroup of patients with BMI $\geq 27\text{kg/m}^2$. The unmet need and expected benefit of treatment were considered to be greatest in this subgroup, as increases in insulin dose are likely to be associated with weight gain, which would further increase cardiovascular event risk in this population. Additionally, DKA risk was observed to be higher in patients with a BMI $< 25\text{kg/m}^2$ compared with the overall study population.⁴ DKA risk was also higher in patients receiving low insulin doses at baseline hence the SPC recommends that dapagliflozin is not used in patients with low insulin need.

There is a lack of longer term data supporting continued benefit of treatment with dapagliflozin beyond 52 weeks and evidence suggests a possible waning of treatment effect on HbA1c raising uncertainty about the duration of effect. There is a lack of evidence to demonstrate a benefit of treatment with dapagliflozin in terms of diabetes-related complications in this patient group. However, a sustained decrease in HbA1c has been previously correlated with a decrease in mortality in patients with type 1 diabetes.⁴ There is some evidence SGLT-2 inhibitors are associated with a reduction in the risk of major adverse cardiovascular events in high risk patients with type 2 diabetes.^{8,9} It is unclear if these findings are generalisable to the type 1 diabetes population.

The indirect evidence, comparing dapagliflozin to off-label metformin, was based on the full study populations and was therefore broader than the licenced indication. There were important methodological and clinical differences between the studies which contributed data to the metformin node of the network and between the metformin studies and the dapagliflozin studies. These differences make the results of the comparisons uncertain.

The EMA and SPC advise that only motivated and educated type 1 diabetes patients who are committed to monitoring their ketone levels and have close contact with a specialist doctor or nurse should be treated with dapagliflozin.¹ The strict monitoring of hypoglycaemia and DKA in the DEPICT studies may not be likely in practice, as a consequence higher rates of DKA may be seen in Scottish practice.^{4, 10}

Dapagliflozin is likely to be a treatment alternative only for limited number of patients with type 1 diabetes, for example those with substantial problem with glucose variability and for those in whom an increase of the insulin dose would not be appropriate. Clinical experts consulted by SMC highlighted that dapagliflozin may be of value in well-motivated patients trying to achieve tight glycaemic control and committed to control ketone levels but experiencing problems with weight gain.

Summary of comparative health economic evidence

The company submitted a cost utility analysis comparing dapagliflozin 5mg (as an add-on to insulin) to standard of care (SoC), for the treatment of insufficiently controlled type 1 diabetes in patients with BMI $\geq 27\text{kg/m}^2$, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy. Based on SMC expert responses insulin is likely to be the primary comparator.

A patient level micro simulation model was submitted (Cardiff Type 1 Diabetes Model). The model simulates disease progression of individual patients across a series of discrete time periods. A lifetime horizon of 80 years was used. Patients in the model enter with predefined baseline characteristics and modifiable risk factors (which were derived from the pooled DEPICT studies).^{2,3} A key feature of the model is the use of risk equations to link changes in risk factors to the

incidence of long term type 1 diabetes complications. Risk equations were derived primarily from DCCT and EDIC, two long term studies which determined the incidence and predictors of cardiovascular disease (CVD) as well as other diabetic complications.¹¹⁻¹⁴ Complications included in the model were microvascular events such as nephropathy, retinopathy and neuropathy. Cardiovascular events and hypoglycaemia events were also captured. The difference in treatment effect is based on the results of the pooled DEPICT studies. Dapagliflozin was associated with a -0.26% reduction in HbA1c and -3.15kg reduction in weight compared to SoC, based on pooled study data at 52 weeks. This treatment effect is assumed to be maintained throughout the model duration.

Utility values and disutilities associated with diabetes complications were included in the model and were taken from several published literature sources which included patients with type 1 and type 2 diabetes. Values were elicited from patients primarily using the EQ-5D instrument and UK tariffs were used. Baseline utility of a patient with type 1 diabetes was estimated to be 0.865 whilst key disutilities were -0.075 and -0.008 for CVD and unit of BMI increase respectively. Disutility associated with DKA was not considered in the base case analysis.

Treatment costs associated with dapagliflozin 5mg and insulin were included in the analysis. Insulin costs were included in both treatment arms and the insulin cost per unit was based on a weighted average cost of various existing insulin formulations (basal bolus and intermediate-acting). The company assumed that 95% of patients would receive basal bolus insulin, whilst 5% would receive intermediate-acting insulin. Costs associated with diabetes related complications were included in the model and derived from various published sources.^{15, 16} No administration costs were included as treatments were assumed to be self-administered by patients. The base case did not consider costs associated with ketone monitoring. Adverse event costs associated with urinary tract infection, genital infection, DKA and severe and non-severe hypoglycaemia were included in the analysis. Only patients in the dapagliflozin arm were capable of discontinuing.

Base case and key scenario analyses results are included in the tables below.

Table 3: Base case results

Base case analysis	Incremental costs	Incremental QALYs	ICER (£/QALY)
Dapagliflozin vs SoC	£1,691	0.29	£5,849

SOC = standard of care, QALY = quality-adjusted life year, ICER = incremental cost-effectiveness ratio

Table 4: Key scenario analyses

Scenario	ICER (£/QALY)
1. Waning of HbA1c for dapagliflozin (HbA1c is assumed to return to baseline levels at year 2). Patients are also assumed to remain on treatment and the time horizon is reduced to 40 years.	£33,077
2. Dapagliflozin versus metformin	£16,329
3. No discontinuation on dapagliflozin	£8,985

4. Annual DKA rate (6% in SoC arm and 10% in dapagliflozin arm). Monitoring costs assumed to be the same in both arms.	£7,671
5. Ketone monitoring included for both arms (cost of ketone strips assumed to be 3 times higher than SoC, that is £49.11)	£6,885
6. DKA mortality included (4% of events end in death)	£5,867
7. Disutility associated with a DKA event (-0.012)	£5,865
8. Time horizon 30 years	£6,630
9. Time horizon 40 years	£5,869

SOC = standard of care, DKA = diabetic ketoacidosis, ICER = incremental cost-effectiveness ratio

There were a number of weaknesses with the analysis which included the following;

- The reduction in HbA1c from the clinical studies and used in the economic model may be considered modest. The economic results should therefore be interpreted with caution.
- In the economic model, change in HbA1c at week 52 is assumed to be maintained over time. Given the lack of long term data, this assumption is uncertain. The company provided a scenario analysis which introduces a waning of the HbA1c treatment effect with dapagliflozin whereby HbA1c levels return to baseline by year 2. These results, which also include a reduced 40 year time horizon, are presented in scenario 1.
- The economic model assumes that weight reduction associated with dapagliflozin is maintained over the duration of the modelled time horizon. Given the lack of long term data supporting a maintained weight reduction, this assumption may not be appropriate. The company provided additional scenario analyses where weight change was assumed to return to baseline levels at various time points. The most conservative scenario assumed that weight change in year 1 is maintained until year 2 before returning to baseline levels in year 3. This increased the ICER to £8,084.
- The incidence of DKA used in the economic model may underestimate the likely incidence in Scottish clinical practice. Within the economic model, annual DKA rates were estimated to be 1.7% and 1.0% in the dapagliflozin arm and SoC arm respectively (based on the pooled DEPICT studies). However, as patients within the DEPICT studies received frequent monitoring, this may not be representative of the incidence expected in Scottish clinical practice. The company provided a scenario analysis which assumes an annual rate of 6% in the SoC arm and 10% in the dapagliflozin arm. As noted in Table 4 above results were not overly sensitive to this analysis.

Despite the uncertainties outlined above, the economic case has been demonstrated.

Summary of patient and carer involvement

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

- We received a patient group submission from Diabetes Scotland, which is a Scottish Charitable Incorporated Organisation (SCIO).
- Diabetes Scotland has not received any pharmaceutical company funding in the past two years.
- Diabetes impacts on every aspect of daily living from work and relationships to physical activity. It is more than a physical health condition, it has behavioural, psychological, and social impacts. On average a person living with type 1 diabetes will make over 100 diabetes-related decisions each day. The fear and anxiety associated with hypoglycaemia cannot be under estimated. Many individuals will 'run' their blood glucose 'high' to avoid such episodes and consequently increase the risk of developing life changing complications such as sight loss, stroke and amputation.
- The standard treatment for type 1 diabetes is insulin replacement therapy. People living with diabetes also have to understand the nutritional value of the food and fluids, matching insulin dosage to the carbohydrates in the food they eat and drink. There is a cohort of patients who have sub-optimal control and self-management, who fail to reach glycaemic targets and may be overweight or obese. This increases their risk of life changing complications.
- Dapagliflozin, as an adjunct to basal bolus insulin may improve glycaemic management and result in weight loss for some people who previously struggled to achieve optimal self-management. The development of effective non-invasive adjunct therapies that help reduce the risk of the short and long-term complications of type 1 diabetes, improve glycaemic control and ultimately have an impact on quality of life are welcomed.
- The importance of careful monitoring and control of ketones to manage the risk of diabetic ketoacidosis was recognised.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published Management of diabetes: A national clinical guideline (SIGN 116)¹⁷ in March 2010 and updated the guidance in November 2017. The guidance does not include any recommendations for add-on therapies to insulin for the treatment of type 1 diabetes.¹⁷

Additional information: comparators

Insulin therapy alone, insulin therapy plus off-label metformin may sometimes be used.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
dapagliflozin	5mg oral daily	475
metformin (off-label)	500mg to 2000mg oral daily	8 to 31

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 30 May 2019. Listed treatments are add-ons to insulin and insulin cost is not included.

Additional information: budget impact

The submitting company estimated there would be 10,077 patients eligible for treatment in year 1 rising to 11,497 in year 5.

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget impact of dapagliflozin.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 12 July 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine 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.