

dapagliflozin 5mg and 10mg film-coated tablets (Forxiga®)

SMC No. (799/12)

Bristol-Myers Squibb / AstraZeneca

07 September 2012 (*Issued 07 December 2012*)

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

dapagliflozin (Forxiga®) is accepted for restricted use within NHS Scotland.

Indication under review: For use in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Add-on combination therapy

In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

SMC restriction: Dapagliflozin is restricted to use as dual therapy in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycaemic control and a sulphonylurea is inappropriate.

In three phase III randomised, controlled studies, dapagliflozin when added to metformin was non-inferior to a sulphonylurea in combination with metformin, and superior to placebo in terms of glycaemic control, as measured by change in HbA1c. This was accompanied by reductions in body weight and the risk of hypoglycaemia with dapagliflozin treatment was similar to placebo and lower, when compared with sulphonylurea.

In a phase III randomised, controlled study, dapagliflozin treatment, when added to an insulin-containing regimen, was associated with; greater reductions in HbA1c, in body weight; and similar rates of hypoglycaemia when compared with placebo.

The submitting companies did not present a sufficiently robust economic analysis to gain acceptance by SMC for use in addition to insulin in patients who have inadequate glycaemic control.

Dapagliflozin is also licensed for use as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered

inappropriate due to intolerance. The manufacturers' submission related only to the use of dapagliflozin when used as dual therapy in combination with either metformin or insulin. SMC cannot recommend the use of dapagliflozin as monotherapy.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Dapagliflozin is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy

In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Dosing Information

The recommended dose is 10mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin. When dapagliflozin is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

Tablets should be swallowed whole, with or without food.

Product availability date

19th November 2012

Summary of evidence on comparative efficacy

Dapagliflozin is a novel anti-diabetic medicine, which inhibits the sodium-glucose co-transporter 2 (SGLT2) located in the kidney. Dapagliflozin improves fasting and post-prandial glucose levels by increasing urinary glucose excretion through inhibition of 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. Dapagliflozin has a marketing authorisation for use in adults with type 2 diabetes mellitus to improve glycaemic control (i) as monotherapy (when diet and exercise do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance) and (ii) as add-on combination therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

The submitting companies have requested that the Scottish Medicines Consortium (SMC) considers dapagliflozin when positioned for use:

- as dual therapy in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycaemic control
- or in addition to insulin, alone or with other oral anti-diabetic medicines, when the underlying treatment regimen, which includes insulin, does not provide adequate glycaemic control.

Evidence to support the use of dapagliflozin as dual therapy in combination with metformin is from three similarly designed multi-centre, randomised, double-blind, controlled phase III studies: a non-inferiority study in comparison with glipizide,^{1,2,3} and two placebo-controlled studies.^{4,5,6} In these three studies, efficacy was analysed in the full analysis set, described as randomised patients who had received study treatment and had baseline and at least one post-baseline efficacy measurement. Imputation of missing data used last observation carried forward methodology.

The 52-week non-inferiority study with glipizide recruited adults with type 2 diabetes and inadequate glycaemic control (glycosylated haemoglobin [HbA1c] >6.5% to ≤10%) despite eight weeks treatment with metformin ± another oral anti-diabetic agent (up to half maximum dose), fasting plasma glucose ≤15mmol/L, and C-peptide concentration ≥0.33nanomol/L. In addition to open-label metformin, patients were randomised 1:1 to receive once daily oral doses of dapagliflozin (n=406) 2.5mg or glipizide (n=408) 5mg, and up-titrated over 18 weeks to 10mg or 20mg, respectively, or the maximum tolerated dose of each. Treatment was discontinued if calculated creatinine clearance was <60mL/min or if glycaemic control did not meet pre-specified thresholds. The primary outcome was the change from baseline to week 52 in HbA1c level with a pre-specified non-inferiority margin of 0.35%.¹

The primary outcome was the same in both groups: -0.52% (95% confidence interval [CI]: -0.6 to -0.44%), a mean difference of 0.00% (95% CI: -0.11 to 0.11). The upper limit of the 95% CI was less than 0.35% so non-inferiority was demonstrated.¹

Secondary outcomes included the adjusted mean change in body weight after 52 weeks. The mean change in the dapagliflozin group was -3.22kg compared with 1.44kg in the glipizide group, a significant treatment difference of -4.65kg (95% CI: -5.14 to -4.17). The proportion of patients achieving at least a 5% reduction in body weight was 33% in the dapagliflozin group and 2.5% in the glipizide group, p<0.0001.¹

In the ongoing extension of this study, two year interim results showed the change in HbA1c in the dapagliflozin group (n=315) was -0.32% (95% CI: -0.42 to -0.21) compared with -0.14% (95% CI: -0.25 to -0.03) in the glipizide group (n=309). Weight loss was sustained in the dapagliflozin group (-3.7kg) compared with weight gain in the glipizide group (1.36kg) and the proportion of patients with at least 5% weight loss was 24% versus 2.8%, respectively.^{2,3}

A placebo-controlled study recruited adults with inadequately controlled type-2 diabetes, despite a stable dose of metformin of ≥1,500mg/day for at least eight weeks. Patients were randomised 1:1:1:1 to dapagliflozin 2.5mg (n=135), 5mg (n=133), 10mg daily (n=132) or placebo (n=134), and continued open-label metformin at pre-study dose. Rescue therapy was permitted with pioglitazone or acarbose with subsequent results treated as missing. The primary outcome was change from baseline to week 24 in HbA1c. After 24 weeks, patients receiving dapagliflozin 10mg daily had a mean reduction in HbA1c of 0.84% from a baseline of 7.92%, compared with a reduction of 0.30% from a baseline of 8.11% for placebo a treatment effect of -0.54% (95% CI: -0.74 to -0.34). Durability of response was reported over two years with a change in HbA1c of -0.78% in the dapagliflozin group (n=57), and 0.02% in the placebo group (n=28), a treatment difference of -0.80% (95% CI: -1.08 to -0.52%). A significantly greater proportion of patients in the dapagliflozin group, 41%, achieved a target HbA1c <7.0% after 24 weeks, a secondary endpoint, compared with placebo, 26%.^{4,6}

A placebo-controlled study investigating weight changes in patients with inadequately controlled type-2 diabetes, despite a stable dose of metformin (≥1,500mg/day for ≥12 weeks) recruited

women aged 55 to 75 years who were postmenopausal for ≥ 5 years, and men aged 30 to 75 years. Patients were randomised 1:1 to dapagliflozin 10mg daily or placebo, in addition to open label metformin at pre-study dose. Rescue therapy was permitted with sitagliptin with subsequent results treated as missing. The primary outcome was change in body weight from baseline to week 24. Dapagliflozin treatment (n=89) was associated with a significant reduction in body weight after 24 weeks compared with placebo (n=91): -2.96kg and -0.88kg, respectively, a treatment difference of -2.08kg (95% CI: -2.84 to -1.32). This was accompanied by statistically significant changes in waist circumference, treatment effect of -1.52cm. The effect on body weight was maintained in an interim analysis, at week 50, of the extension phase of this study.⁵

The addition of dapagliflozin to an insulin-containing regimen was investigated in a multi-centre, randomised, double-blind, placebo-controlled phase III study. Adults with inadequately controlled type 2 diabetes (HbA1c $\geq 7.5\%$ and $\leq 10.5\%$) and body-mass index $\leq 45\text{kg/m}^2$ were recruited if they had been receiving a stable insulin dose of ≥ 30 units/day for the previous eight weeks and up to two oral antidiabetic agents at a stable dose. Patients continued on their pre-study therapy, and were randomised 1:1:1:1 to dapagliflozin 2.5mg (n=202), 5mg (n=211), 10mg daily (n=194) or placebo (n=193). Insulin dosage could be titrated by no more than 5 units ($<10\%$) according to pre-specified thresholds, whereas oral antidiabetic drug dosages could be reduced only if there was still some risk of hypoglycaemia despite discontinuation of insulin.⁷

The primary outcome was the change in HbA1c from baseline to week 24 evaluated in the full analysis set (randomised patients who had received study treatment and had baseline and at least one post-baseline efficacy measurement) using a mixed-model repeated measures approach. The change in HbA1c with dapagliflozin 10mg was -0.96%, compared with -0.39% for placebo, a significant treatment difference of -0.57% (95% CI: -0.72 to -0.42) that was maintained at week 48, -0.54% (-0.70 to -0.38), and at week 104, -0.65% (-0.90 to -0.41).⁷

Dapagliflozin was associated with a significant placebo-adjusted change in body weight at 24 and 48 weeks: -2.04kg and -2.43kg, respectively. Mean daily insulin requirement increased in the placebo group, whereas in the dapagliflozin group it was stable. At 24 weeks, the treatment-difference in mean insulin daily dose was -6.82 units, and at 48 weeks it was -11.25 units. At 104-weeks the difference was -19.17 units.⁷

Summary of evidence on comparative safety

Comparative safety is from the non-inferiority study versus glipizide in which, after 52 weeks, similar proportions of patients reported reported treatment-related adverse events (AE) (27% in each group). Serious AE were reported in 8.6% (35/406) of patients in the dapagliflozin group (judged to be treatment-related in six patients) and by 11% (46/408) of patients in the glipizide group (judged to be treatment-related in four patients), with similar rates of discontinuation due to serious AE (2.2% versus 2.0%, respectively).

Dapagliflozin was associated with significantly fewer hypoglycaemic events (3.4%) compared with glipizide (40%). The majority of events were considered to be minor episodes (1.7% in the dapagliflozin group, and 36% in the glipizide group). There was a higher reported incidence of suspected urinary tract infection (11% versus 6.4%), suspected genital infection (12% versus

2.7%), and reduced calculated creatinine clearance (Cockcroft Gault, 4.2% versus 1.7%) in the dapagliflozin group compared with glipizide.

One patient in the dapagliflozin group experienced drug-induced hepatitis, which improved with discontinuation and resolved after six months of immunosuppressant treatment.¹

Throughout the clinical development programme, the reported incidence of unspecified or malignant tumours was similar between those treated with dapagliflozin (1.47%) and control (1.35%). There was an imbalance in the proportion of patients with prostate, bladder or breast cancer between groups but this was not statistically significant. Causality has not been established for any of these cancers.⁸

Summary of clinical effectiveness issues

Dapagliflozin is the first sodium glucose transporter 2 antagonist licensed to improve glycaemic control in type 2 diabetes in the UK. The submitting companies have requested that SMC considers dapagliflozin when positioned for use: (i) as dual therapy in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycaemic control; or (ii) in addition to insulin, alone or with other oral anti-diabetic medicines, when the underlying treatment regimen, which includes insulin, does not provide adequate glycaemic control.

Current treatment guidelines recommend that for dual therapy with metformin, the following options should be considered: sulphonylurea, thiazolidinedione, or dipeptidyl-peptidase-4 (DPP-4) inhibitors. Medicines licensed for use as add-on treatment to insulin include pioglitazone, exenatide, and selected DPP-4 inhibitors (sitagliptin and saxagliptin). Pioglitazone and exenatide have both been accepted by SMC for use as add-on treatment to insulin and pioglitazone is recommended in NICE guidance. The DPP-4 inhibitors have been not recommended by SMC for use as add-on treatment to insulin due to non-submission.

The primary outcome measure used in most studies was the change in HbA1c. HbA1c is the most widely accepted measure of long-term glycaemic control and lowering HbA1c is associated with a reduction in the risk of microvascular and macrovascular complications of diabetes. The way in which HbA1c results are expressed in the UK has changed recently; results are now reported as mmol/mol rather than as a percentage. The equivalent of the HbA1c targets of 6.5% and 7.5% are 48mmol/mol and 58mmol/mol in the new units with the non-diabetic reference range of 4.0% to 6.0% being 20mmol/mol to 42mmol/mol.

Dapagliflozin was demonstrated to be superior to placebo for change in HbA1c and body weight in both settings (dual therapy with metformin, and as part of an insulin-containing regimen). When used in combination with metformin dapagliflozin was non-inferior to glipizide in terms of glycaemic control (HbA1c at 52 weeks) and also significantly reduced body weight. Evidence for durability of response comes from the results of two-year extension phases from three of the four key studies.

An additional benefit of dapagliflozin of relevance to patients with type 2 diabetes is the reduced risk of hypoglycaemia compared with glipizide. However, consistent with its mechanism of action there is an increased incidence of urinary and genital infections associated with dapagliflozin.

There are some limitations to the clinical evidence. While HbA1c has been linked with reductions in the long-term complications of diabetes, there are no direct health outcome data demonstrating that dapagliflozin in combination with insulin or metformin reduces micro- and/or macro-vascular complications.

In the pivotal insulin-add on study, the insulin dose was not titrated to any target HbA1c, rather it was adjusted to minimise the risk of hypoglycaemia, or up-titrated by no more than 5 units (or 10%), in response to fasting plasma glucose levels. Titration to HbA1c was permitted during the double-blind extension phases of the study.⁷

The mean age of the populations recruited across all the studies ranged from 53 to 61, whereas the recent Scottish Diabetes Survey reported that 50% of patients with type 2 diabetes in Scotland are aged over 65 years. In the insulin-add-on study, a minority of patients were prescribed basal insulin (16 to 23%), and the majority were prescribed a bolus, or basal-bolus, insulin regimen.⁷ This may reduce the external validity of the study results to patients prescribed basal insulin, which is the initial insulin regimen recommended by UK guidelines. The metformin add-on study in which changes in body mass was the primary endpoint excluded pre- and peri-menopausal women.⁵ This measure (to avoid confounding of safety in relation to changes in bone mineral density) reduced the generalisability of the study results to this patient group.

The pharmacological effect of dapagliflozin depends on adequate renal function, and efficacy is reduced in patients who have moderate renal impairment and is probably absent in patients with severe renal impairment. Dapagliflozin is therefore not recommended in patients with moderate to severe renal impairment. Renal function should be monitored before initiating treatment and then at least annually, depending on concomitant medication and renal status. If renal function falls below a creatinine clearance $<60\text{ml/min}$ or estimated glomerular filtration rate $<60\text{ ml/min/1.73 m}^2$, dapagliflozin treatment should be discontinued.⁸

There were no data relating to treatment-effects on quality of life.

To support the economic case, network meta-analyses (NMA) indirectly compared dapagliflozin with anti-diabetic medicines relevant to the selective indications under consideration, DPP-4 inhibitors and pioglitazone when used as (1) add-on to metformin and (2) add-on to insulin position. Three networks were presented: add-on to metformin (24 week); add-on to metformin (52 week); and add-on to insulin (24 week). SMC expert statistical advice indicated that the results of the insulin NMA were limited by the low number of studies ($n=4$). A limitation of the analysis affecting internal validity was that the baseline HbA1c in the single pioglitazone study was higher than in three other included studies.

The key findings from the add-on to metformin NMA were:

- Compared to DPP-4 inhibitors and pioglitazone, dapagliflozin was associated with significantly greater weight loss. No significant differences were found in HbA1c, systolic blood pressure or the risk of hypoglycaemia.
- Compared to sulphonylurea, dapagliflozin was associated with a similar reduction in HbA1c but with improved weight control, lower systolic blood pressure, and reduced risk of hypoglycaemia. These findings support those from the comparative non-inferiority study of dapagliflozin versus sulphonylurea.

Summary of comparative health economic evidence

The submitting companies presented cost-utility analyses to address the use of dapagliflozin in the following situations:

- (a) Dapagliflozin as an add-on to metformin compared to the current treatment options of sulphonylurea (SU), DPP-4 inhibitors or pioglitazone in type 2 diabetic patients for whom metformin alone (with diet and exercise) does not provide adequate control; and
- (b) Dapagliflozin as an add-on to insulin (with or without other oral anti-diabetic agents) compared to DPP-4 inhibitors when the underlying treatment regimen including insulin does not provide adequate control.

The comparators as add-on to metformin appear appropriate given current clinical guidelines. For the DPP-4 inhibitors it should be noted that SMC has issued not recommended advice for sitagliptin and saxagliptin as an add-on therapy to insulin and feedback from SMC clinical experts suggests that DPP-4 inhibitor use is not standard in this setting.

In each case, a discrete event simulation model was used to project costs and outcomes over a lifetime (40 year) time horizon. The model structure, which was the same for each analysis and similar to other economic models in diabetes, used changes in risk factors (HbA1c, systolic blood pressure, weight and cholesterol levels) to predict changes in longer term micro- and macro-vascular complications such as heart disease, stroke, blindness and renal disease.

The effects of dapagliflozin and the comparator regimens on risk factors were taken from the non-inferiority study for the comparison with sulphonylurea, and from the network meta-analyses for the other comparisons. For the metformin add-on therapy analysis, estimates of effect for some risk factors were available from the network meta-analysis at both 24 weeks and 52 weeks. Changes in weight were an important influence in the model and the base case assumed that weight loss with dapagliflozin is maintained for 2 years and after this time reverts to the baseline weight and then rises at a rate of 0.1kg per year. A gain in utility of 0.0171 was also included for each unit decrease from weight loss. Given the assumptions made, the model estimates a continuing weight advantage to dapagliflozin over comparator treatments for the duration of the model.

Utility values were taken from a commonly-used published paper but the impact of weight changes on quality of life were taken from a bespoke utility study which estimated a utility gain of 0.0171 for each unit decrease in BMI and a disutility of -0.0472 for each unit increase. Resource use was estimated from a published United Kingdom Prospective Diabetes Study (UKPDS) paper.

The results of the analyses are shown below:

	As add-on treatment to insulin. Dapagliflozin versus:	As add-on treatment to metformin. Dapagliflozin versus:		
	DPP-4	SU	DPP-4	Pioglitazone
Incremental cost	£538	£1,335	-£143	-£80
Incremental quality adjusted life years (QALYs)	0.126	0.50	0.02	0.4
Incremental cost effectiveness ratio (ICER)	£4,268	£2,689	Dapagliflozin dominant	Dapagliflozin dominant

A good range of sensitivity analysis was provided and this showed the results were upwardly sensitive to a range of variables or assumptions. Particular sensitivity was seen when using a more conservative published value for weight gain disutility (Bagust, 0.0061) and assuming weight for treatment and comparator therapy converge over time. There was also sensitivity when using the results of the 52-week network meta-analysis in the metformin add-on analysis versus DPP-4 inhibitors and pioglitazone.

A key concern was the comparatively large disutility assumed for weight gain compared to other published estimates used in SMC submissions and therefore the Committee felt the more conservative Bagust estimate would have been more appropriate to have used in the base case. While the base case cost-effectiveness ratios are comparatively low even when one-way sensitivity analysis using the Bagust values were used, a limitation was that all results had incorporated non-significant differences into the analysis. Revised analysis was provided from the companies to show the combined impact of excluding non-significant differences and using the Bagust values to give a set of base case values, as shown below:

	As add-on treatment to insulin. Dapagliflozin versus:	As add-on treatment to metformin. Dapagliflozin versus:		
	DPP-4	SU	DPP-4	Pioglitazone
Incremental cost	£294	£1,663	£310	£448
Incremental quality adjusted life years (QALYs)	0.04	0.099	0.031	0.098
Incremental cost effectiveness ratio (ICER)	£,7,333	£,16,786	£10,000	£4,552

SMC clinical experts suggested that it may have been more appropriate to assume convergence of weight over time. The submitting companies provided revised analysis to show the impact of including this assumption into the revised base case values presented above, and the impact was to increase the cost per QALYs. The cost per QALY figures were £25,153,

£10,000 and £6,661 for the comparisons against sulphonylurea, DPP-4 inhibitors and pioglitazone respectively. These figures were used as the basis of the SMC decision.

While these cost-effectiveness ratios are broadly acceptable, there were a number of issues with the analyses:

- For the insulin add-on comparison, there are some limitations associated with the indirect comparison, as noted above. In addition, SMC clinical experts have suggested that DPP-4 inhibitors are not the predominant treatment comparators. As such, the analysis is not considered robust.
- In the metformin add-on comparison, sensitivity analysis using of the 52-week NMA results indicated that there was some upward uncertainty from incorporating these data.
- As with recent SMC submissions using diabetes economic models, committee members expressed some concerns regarding the validity of using short term outcome measures to proxy long term treatment effects.

Given these issues, on the basis of the revised base case analyses presented, the economic case was considered to have been demonstrated for the metformin add-on analysis against DPP-4 inhibitors and pioglitazone but not against sulphonylureas. The Committee considered that the economic case had not been demonstrated for the insulin add-on comparison.

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

Summary of patient and public involvement

A Patient Interest Group Submission was received from Diabetes UK Scotland.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published updated guidance on the “Management of diabetes” in March 2010. 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). In the treatment algorithm devised in the guideline, in patients with type 2 diabetes mellitus the following treatments are considered as alternative second-line options to sulphonylureas; thiazolidinedione (eg pioglitazone) if there is no risk of congestive heart failure and if hypoglycaemic episodes are a concern; dipeptidyl peptidase-IV inhibitors (eg sitagliptin, saxagliptin, vildagliptin, linagliptin) if hypoglycaemic episodes or weight gain is a concern. Use of glucagon like peptide-1 agonists (eg liraglutide, exenatide) can be considered as a third-line option. 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 Clinical Excellence published NICE Clinical Guideline 87 – Type 2 diabetes - newer agents, in May 2009. The guideline recommended that patients using basal insulin regimens (e.g. neutral protamine Hagedorn or long-acting analogues) should 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 guidelines predate the licensing of dapagliflozin.

Additional information: comparators

Medicines licensed for type 2 diabetes that can be used in combination with metformin include: sulphonylureas, DPP-4 inhibitors, thiazolidinediones, glucagon-like peptide-1 agonists, meglitinides, alpha glucosidase inhibitors.

Therapeutic approaches aimed at achieving glycaemic control in patients with type 2 diabetes taking insulin (usually with metformin and/or sulfonylurea) include: review and modification of lifestyle; titration of insulin dose; intensification of insulin regimen with introduction of additional daily injections; addition of oral adjunct (pioglitazone, saxagliptin or sitagliptin). Saxagliptin and sitagliptin have been not recommended by SMC for use in NHS Scotland for this indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Dapagliflozin	10mg orally once daily	476
Liraglutide	0.6mg to 1.8mg once daily by subcutaneous injection	476 to 1,428
Tolbutamide	500mg to 2g orally daily	300 to 1,199
Exenatide prolonged-release	2mg once weekly by subcutaneous injection	954
Exenatide	5 micrograms to 10 micrograms twice daily by subcutaneous injection	828
Sitagliptin*	100mg orally once daily	432
Linagliptin	5mg orally once daily	432
Vildagliptin	50mg orally twice daily	413
Saxagliptin*	5mg orally once daily	411
Nateglinide	60mg to 180mg orally before each meal**	295 to 336
Pioglitazone	15mg to 45mg orally once daily	215 to 319
Acarbose	50mg to 200mg orally three times daily	85 to 311
Repaglinide	500 micrograms to 4mg orally before each meal **	50 to 200
Gliclazide modified release	30mg to 120mg orally once daily	33 to 133

Glipizide	2.5mg to 20mg orally daily	14 to 116
Gliclazide	40mg to 320mg orally daily	7 to 55
Glibenclamide	5mg to 15mg orally once daily	12 to 37
Glimepiride	1mg to 4mg orally once daily	14 to 18

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 09 July 2012 except dapagliflozin (from company's submission).

* Licensed but not recommended by SMC for use in combination with insulin. ** Costs based on three meals a day

Additional information: budget impact

As an add on to metformin

The submitting companies estimated the population eligible for treatment to be a constant 57,749 in all five years with an estimated uptake rate of 0.77% in year 1 and 7.04% in year 5. The gross impact on the medicines budget was estimated to be £210k in year 1 and £1.93m in year 5. As other drugs were assumed to be displaced the net medicines budget impact is assumed to be £19k and £175k in years 1 and 5 respectively.

As an add on to insulin

The submitting companies estimated the population eligible for treatment to be a constant 335 in all five years with an estimated uptake rate of 1% in year 1 and 9.20% in year 5. The gross impact on the medicines budget was estimated to be £3k in year 1 and £24k in year 5. As other drugs were assumed to be displaced the net medicines budget impact is assumed to be £0.1k and £1k in years 1 and 5 respectively.

References

The undernoted references were supplied with the submission.

- 1) Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycaemic control with metformin: A randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care* (2011); 34: 2015-22 (plus web-only supplementary data).
- 2) Del Prato S, Nauck MA, Rohwedder K, Theuerkauf A et al. Long-term efficacy and safety of add-on dapagliflozin vs add-on glipizide in patients with type 2 diabetes mellitus inadequately controlled with metformin: 2-year results. Presented at the 47th Annual Meeting of the EASD, Lisbon, Portugal, September 12 to 16; Abstract 852. 2011
- 3) Nauck M, Del Prato S, Rohwedder K, Theuerkauf A et al. Long-term efficacy and safety of add-on dapagliflozin vs add-on glipizide in patients with T2DM inadequately controlled with metformin: 2-year results. Presented at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, June 24 to 28 2011; Abstract 40-LB. 2011
- 4) Bailey CJ, Gross JL, Pieters A, Bastien A et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin; a randomised, double-blind, placebo-controlled trial. *Lancet* (2010); 375: 2223-33.
- 5) Bolinder J, Ljunggren O, Kullberg J, Johansson L et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycaemic control on metformin. *J Clin Endocrinol Metab* (2012); 97: 1020-31 (plus web-only supplementary data).
- 6) Bailey CJ, Gross JL, Yadav M, Iqbal N et al. Long-term efficacy of dapagliflozin as add-on to metformin in T2DM inadequately controlled with metformin alone. Presented at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, June 24 to 28 2011; Abstract 988-P. 2011
- 7) Wilding JPH, Woo V, Soler NG, Pahor A et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin. *Annals Intern Med* (2012); 156: 405-15 (plus web-only supplemental data)
- 8) Summary of product characteristics for dapagliflozin (Forxiga). Bristol Myers Squibb/AstraZeneca 2012.

This assessment is based on data submitted by the applicant company up to and including **15 November 2012**.

**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_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.