Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

Re-Submission

dapagliflozin 5mg and 10mg film-coated tablets (Forxiga®) SMC No. (799/12)
Bristol-Myers Squibb / AstraZeneca

07 February 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 resubmission

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 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: In combination with insulin, when insulin with diet and exercise, does not provide adequate glycaemic control.

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

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 companies' submission related only to the use of dapagliflozin when used in combination with insulin. SMC cannot recommend the use of dapagliflozin as monotherapy. SMC has previously accepted dapagliflozin for restricted use in combination with metformin.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 10 March 2014

Indication

In adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control 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. 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.

In patients with severe hepatic impairment, a starting dose of 5mg is recommended. If well tolerated, the dose may be increased to 10mg.

Product availability date

November 2012

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. 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.

The submitting companies have requested that SMC considers dapagliflozin when positioned for use in combination with insulin, when insulin with diet and exercise does not provide adequate glycaemic control. SMC has previously accepted the use of dapagliflozin in combination with metformin, when metformin alone with diet and exercise do not provide adequate glycaemic control and a sulfonylurea is inappropriate.

The addition of dapagliflozin to an insulin-containing regimen was investigated in a multi-centre, randomised, double-blind, placebo-controlled phase III study.[1,2] Adults with inadequately controlled type 2 diabetes, glycosylated haemoglobin (HbA1c) ≥7.5% and ≤10.5%, and body-mass index ≤45kg/m^2 were recruited if they had been receiving a stable insulin dose of ≥30units/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. Treatment was continued for 24 weeks, after which patients could continue onto two further double-blind extension phases up to a total of 104 weeks.

The primary outcome of the study was the change in HbA1c from baseline to week 24 evaluated in the full analysis set (randomised patients who received at least one dose of study medication, with baseline data and at least one post-baseline result) using a mixed-model repeated measures approach. At baseline, HbA1c was 8.57% in the dapagliflozin 10mg group, and 8.47% in the placebo

group. After 24 weeks, the change in HbA1c from treatment with dapagliflozin 10mg was -0.96%, compared with -0.39% for placebo, a significant treatment difference of -0.57% (95% confidence interval [CI]: -0.72 to -0.42), p<0.001. This was maintained at week 48, -0.54% (95% CI: -0.70 to -0.38) and at week 104, -0.35% (95% CI: -0.55 to -0.15).

Dapagliflozin 10mg was associated with a significant placebo-adjusted change in body-weight at 24, 48, and 104 weeks: -2.04kg, -2.43kg, and -3.33kg respectively. Mean daily insulin requirements increased in the placebo group, whereas in the dapagliflozin 10mg group they were stable. At 24 weeks, the treatment difference in mean insulin daily dose was -6.8 units, and at 48 weeks, it was -11.2 units. At 104 weeks, the difference was -19.2 units.

Summary of evidence on comparative safety

After 104 weeks, similar proportions of patients reported at least one adverse event: dapagliflozin 10mg 80% (157/196), and placebo 78% (154/197). Treatment-related adverse events occurred in 32% of dapagliflozin patients and in 23% of placebo patients, and they were considered serious in one patient in each group (constipation in the dapagliflozin 10mg group, and renal cancer in the placebo group).[2]

Similar rates of hypoglycaemia were reported for each group: 61% and 62% for dapagliflozin 10mg and placebo, respectively. Only a small proportion of patients (1.5% and 1.0% respectively) had a major hypoglycaemic episode (requiring external assistance). Genito-urinary and renal adverse events were of particular interest with dapagliflozin. Events suggestive of genital infection were recorded in 14% of dapagliflozin 10mg patients, and 3.0% of placebo patients. Dapagliflozin 10mg was associated with a greater incidence of events suggestive of urinary tract infection: 14% compared with 5.6%, respectively. Renal impairment or failure was reported in 3.1% of dapagliflozin patients and 2.0% of placebo patients. Hypotension, dehydration or hypovolaemia was reported in 2.0% of dapagliflozin patients and 1.0% of placebo patients.[2]

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.[3]

Summary of clinical effectiveness issues

Dapagliflozin is the first SGLT2 inhibitor 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 in combination with insulin, when insulin with diet and exercise does not provide adequate glycaemic control. SMC has previously accepted dapagliflozin for use in combination with metformin.

Medicines licensed for use as add-on treatment to insulin include pioglitazone, exenatide, lixisenatide and the dipeptidyl peptidase-4 (DPP-4) inhibitors. The DPP-4 inhibitors have not been recommended for use in NHS Scotland by SMC for this indication, and pioglitazone use has diminished due to safety fears such as bladder cancer, so the submitting companies considered the glucagon-like peptide 1 (GLP-1) agonists, exenatide and lixisenatide, to be the relevant comparators in NHS Scotland.

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, and welcomed additional options to manage glycaemia.

The primary outcome in the pivotal study was a surrogate outcome, change in HbA1c (an accepted measure of long-term glycaemic control). In patients with type 2 diabetes, reduction in HbA1c is associated with a reduction in microvascular and macrovascular complications. Treatment guidelines recommend HbA1c targets in the treatment of diabetes.[4,5] 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.

Addition of dapagliflozin to an insulin-containing regimen was associated with a modest, but clinically significant reduction in HbA1c over 104 weeks compared with placebo. This improvement in glycaemic control was coupled with an additional benefit of weight loss of 2 to 3kg over the 24- to 104-week follow-up in the study. There appears to be a low risk of hypoglycaemia with the use of dapagliflozin; however, due to the mode of action, there is a theoretical increased risk of urinary and genital infections, which was observed in the study.

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

In the pivotal 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 target level was permitted during the double-blind extension phases of the study.

A minority of patients were prescribed basal insulin (16% to 23%), and the majority were prescribed bolus, or basal-bolus insulin regimen. 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.[4,5]

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

An important consideration for this patient group is that the pharmacological effect of dapagliflozin depends on adequate renal function; 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 initiation and then at least annually thereafter. If renal function falls below a creatinine clearance <60mL/min or estimated glomerular filtration rate <60mL/min/1.73m^2, dapagliflozin treatment should be discontinued.[3]

To support the economic case, the submitting company presented several analyses in which dapagliflozin was compared with the GLP-1 agonists, exenatide and lixisenatide:

- A Bayesian network meta-analysis (NMA) in which the network comprised seven randomised, double-blind, controlled studies in adults with type 2 diabetes mellitus with inadequate glycaemic control despite an insulin-containing regimen: four studies involving DPP-4 inhibitors,[7-10] and three single studies of dapagliflozin,[1] exenatide,[11] and lixisenatide.[12] Several outcomes were compared: change from baseline to week 24 (+/- 6 weeks) in HbA1c and body weight; and the proportion of patients experiencing hypoglycaemia.
- Two adjusted indirect comparisons using the Bucher method of dapagliflozin versus exenatide, and dapagliflozin versus lixisenatide. Multiple outcomes were compared: change from baseline in HbA1c, body weight and systolic blood pressure; and the odds ratios of hypoglycaemic episodes, adverse events and serious adverse events.

The results of the NMA found no statistically significant difference between dapagliflozin and the two GLP-1 agonists, and this was supported by the results of the Bucher indirect comparisons.

Limitations in the analyses make cautious interpretation of the results necessary. Potential sources of bias in the comparison arise from differences between the studies. The exenatide study employed an insulin titration-to-target approach,[11] whereas the insulin dose was relatively stable in the other studies. There was heterogeneity between the studies in terms of background regimen, which may have contributed to the differences in baseline insulin dosage amongst the studies.

Summary of comparative health economic evidence

The economic analysis submitted by the company was a cost-minimisation analysis (CMA) comparing oral dapagliflozin with two GLP-1 agonists for the management of type 2 diabetes mellitus as add-on to insulin, when insulin alone, with diet and exercise, does not provide adequate glycaemic control. A one year time horizon was used and the analysis was carried out from an NHS Scotland perspective. The comparators within the analysis are two other GLP-1 agonists: exenatide and lixisenatide (both of which are injected). The comparators are deemed to be appropriate, and SMC has previously considered the comparators to be clinically equivalent.

No direct clinical trials comparing dapagliflozin with exenatide and lixisenatide were found by the submitting company. Therefore, to support the CMA, indirect comparisons were performed based on studies that compared the medicines with placebo. The pivotal studies demonstrated that dapagliflozin was superior to placebo, and the indirect comparisons subsequently found no significant difference between dapagliflozin and either exenatide or lixisenatide.

The economic analysis focussed on the relative costs per patient for dapagliflozin versus exenatide and lixisenatide. Costs included medicine costs, needles costs and the nurse time costs.

In the first year, the base case results were savings associated with dapagliflozin of £460 and £289 per patient over exenatide and lixisenatide respectively. For subsequent years, the savings associated with dapagliflozin were £456 and £275 over exenatide and lixisenatide respectively. The difference in savings is the result of nurse costs incurred, in the first year, to teach patients the administration technique for exenatide and lixisenatide.

Sensitivity analyses were performed around the duration of the economic case. The company's sensitivity analysis showed that potential savings per patient in the comparison between dapagliflozin versus exenatide, range from £444 and £375 (between year one and year five respectively). For the comparison between dapagliflozin and lixisenatide, savings range from £279 to £2312, from year one to year five respectively.

The main uncertainty surrounding the analysis is the titration of the insulin in the exenatide study that may have introduced heterogeneity in the NMA. It should be noted that this approach was previously accepted by SMC. The economic case did not present any uncertainties.

In summary, the economic case for dapagliflozin has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published updated guidance on the "Management of diabetes" in March 2010.[4] 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). 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.[5] 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 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.[6] The statement considered several options of a third agent in combination with metformin and insulin with no specific preference: choice based on patient and drug characteristics.

The guidelines predate the licensing of dapagliflozin.

Additional information: comparators

Alternative pharmacological approaches to insulin regimen intensification aimed at improving glycaemic control of patients with type 2 diabetes already taking insulin include adjunctive treatment with: GLP-1 agonists (exenatide, lixisenatide), DPP-4 inhibitors, or pioglitazone.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Dapagliflozin	**10mg orally once daily**	**476**
Exenatide	5 to 10micrograms twice daily by subcutaneous injection	828
Lixisenatide	Maintenance dose of 20micrograms once daily by subcutaneous injection.	657
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

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 02 Dec 2013. *Not recommended for use in NHS Scotland in combination with insulin.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 55 in year 1 and 1,076 in year 5, with an estimated uptake rate of 0.3% in year 1 and 4.3% in year 5.

The gross impact on the medicines budget was estimated to be £26k in year 1 and £513k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be a saving of £24k in year 1 and a saving of £374k in year 5.

References

The undernoted references were supplied with the submission.

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11) Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Annals of Internal Medicine. 2011; 154: 103-12.

12) Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care. 2013. (published online 01 May 2013 ahead of print).

This assessment is based on data submitted by the applicant company up to and including 09 December 2013.

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.