Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Re-Submission

dapagliflozin 5mg and 10mg film-coated tablet (Forxiga®) SMC No. (799/12)

AstraZeneca

06 June 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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a second re-submission

dapagliflozin (Forxiga®) 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 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: in triple therapy in combination with metformin and sulphonylurea, as an alternative to a dipeptidyl peptidase-4 (DPP-4) inhibitor.

SMC has previously accepted dapagliflozin for 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 combination with insulin, when insulin with diet and exercise, does not provide adequate glycaemic control.

Dapagliflozin is also licensed for use as monotherapy but the company's resubmission did not relate to its use in this setting. SMC cannot recommend the use of dapagliflozin as monotherapy.

Overleaf is the detailed advice on this product.

Co-Vice Chairman,
Scottish Medicines Consortium

Indication

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

10mg 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.

Product availability date

18 December 2013

Summary of evidence on comparative efficacy

Dapagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor licensed for treatment of adults with type 2 diabetes in combination with other glucose-lowering medicinal products.[1] SMC has previously accepted dapagliflozin 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;[2] and in combination with insulin, when insulin with diet and exercise, does not provide adequate glycaemic control.[3] This submission relates to a change to the marketing authorisation to include a dapagliflozin 'triple therapy' regimen in combination with metformin and sulphonylurea. The company has requested that SMC considers dapagliflozin in adults with type 2 diabetes poorly controlled on metformin plus sulphonylurea, as an alternative to a dipeptidyl peptidase-4 (DPP-4) inhibitor.

This change to the marketing authorisation is based on a double-blind phase III study in 218 adults with type 2 diabetes inadequately controlled (glycosylated haemoglobin, HbA1c 7.0% to 10.5%) on metformin (at least 1,500mg daily) and sulphonylurea (maximum tolerated and at least half the maximum dose) at stable doses for at least 8 weeks. They were randomised equally to dapagliflozin 10mg once daily or placebo for 24 weeks. The primary endpoint was adjusted mean change in HbA1c from baseline to week 24 in the full analysis set, which included all randomised patients who received at least one dose of study drug and had baseline and at least one post-baseline value for at least one efficacy variable. The least square (LS) mean change from baseline to week 24 in HbA1c was significantly greater with dapagliflozin compared with placebo: -0.86% versus -0.17%, with between treatment difference of -0.69% (95% CI: -0.89 to -0.49). For the secondary outcomes, LS mean changes from baseline to week 24 (week 8 for systolic blood pressure, SBP) were significantly greater with dapagliflozin compared with placebo, with between treatment differences of -1.9mmol/L (95% CI: -2.4 to -1.3) for fasting plasma glucose (FPG), -2.07kg (95% CI: -2.79 to -1.35) for body weight, and -3.76 mmHg (95% CI: -7.05 to -0.48) for seated SBP.[4-6]

Two phase III studies recruited men aged at least 45 years and women aged at least 50 years with type 2 diabetes inadequately controlled on current therapy and cardiovascular disease, with one of these studies (study 18) also requiring that patients have hypertension. They were randomised equally to double-blind dapagliflozin 10mg daily or placebo for 24 weeks.[7-10] In study 18 and 19 there were 25% (227/914) and 22% (214/962) of patients taking metformin and a sulphonylurea at baseline. Within these subgroups, in the respective dapagliflozin and placebo treatment arms mean changes from baseline to week 24 (between treatment difference) in HbA1c were -0.6% and 0% (-0.5%; 95% CI: -0.7 to -0.4) in study 18; -0.6% and -0.1% (-0.5%; 95% CI: -0.7% and -0.3%) in study 19. Mean change from baseline to week 24 (between treatment difference) in body weight was -2.2kg and 0kg (-2.2kg; 95% CI: -2.9 to -1.5) in study 18; -1.9kg and -0.8kg (-1.1kg; 95% CI -1.8 to -0.3) in study 19.[11]

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

Summary of evidence on comparative safety

Adverse effects in triple therapy appear consistent with the established adverse events profile. In the phase III study there were similar rates of adverse events in the respective dapagliflozin and placebo groups: 49% and 51%. Adverse events of special interest included; hypoglycaemia, urinary tract infection, genital infection and kidney infection and renal impairment/failure. More patients in the dapagliflozin groups experienced hypoglycaemia: 13% versus 3.7%. In the respective groups genital infection was reported by 6 versus 0 patients; urinary tract infections were reported by 6.4% of patients in each group.[4,5,6]

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

Summary of clinical effectiveness issues

In a phase III study dapagliflozin was superior to placebo, in combination with metformin and sulphonylurea, for control of HbA1c.[4-6]

HbA1c is an established measure of blood glucose control over the preceding two to three months. 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 7.5% are 48mmol/mol and 58mmol/mol in the new units.

There are no direct comparative data with DPP-4 inhibitors. Therefore network meta-analyses (NMA) were used to compare dapagliflozin in combination with metformin and sulphonylurea to DPP-4 inhibitors in combination with metformin and sulphonylurea in terms of HbA1c, weight, SBP and hypoglycaemia. These included data from placebo-controlled studies of linagliptin, sitagliptin and saxagliptin, but not vildagliptin. The full NMA included these medicines and all other possible comparators: glucagon-like peptide-1 (GLP-1) agonists, alpha-glucosidase inhibitors, meglitinides, thiazolidinediones and insulin. Decision-focused sensitivity analyses that included data for only dapagliflozin, DPP-4 inhibitors and GLP-1 agonists are relevant for this submission. This indirect comparison has some weaknesses including heterogeneity and the omission of a potentially relevant study of vildagliptin but overall the conclusions were considered to be valid.

Clinical experts consulted by SMC considered that the place in therapy of dapagliflozin is as an alternative to DPP-4 inhibitors in patients with inadequate glycaemic control on metformin plus sulphonylurea. They consider that dapagliflozin is a therapeutic advancement due to its novel

mechanism of action and potential beneficial effects on weight, although long-term data for the latter are not available.

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

Summary of comparative health economic evidence

The company submitted a cost- utility analysis for the evaluation of adult patients with type 2 diabetes, comparing dapagliflozin in combination with metformin and sulphonylurea to the DPP-4 inhibitor class, which includes sitagliptin, saxagliptin, linagliptin and vildagliptin in addition to metformin and sulphonylurea.

A discrete events simulation model was used in the analysis. The model simulated a cohort of patients over a 40 year time horizon. Patients entered the model with a set of baseline characteristics and modifiable risk factors for long run micro-vascular complications including blindness, amputation and nephropathy and macro-vascular complications including ischemic heart disease, myocardial infarction, congestive heart failure and stroke. At the end of the first 6 month cycle, risk equations derived from the United Kingdom Progressive Diabetes Study (UKPDS) were used to determine the occurrence of the fatal and non-fatal complications as well as non-cardiovascular all cause diabetes deaths. The effect of a change in body weight and impact on body mass index (BMI) is also incorporated in the model via the risk of experiencing cardiovascular complications.

The clinical evidence used to support the comparison of dapagliflozin versus DPP-4 inhibitors came from the results of the NMA described above which examined various outcome measures including HbA1c, weight, SBP and hypoglycaemia. It should be noted that as with previous diabetes models assessed by SMC, there is some uncertainty regarding the use of surrogate outcomes as a means of predicting long term treatment effects.

Utility values associated with complications, hypoglycaemia, weight change and urinary tract infection/genital infection adverse events were included in the analysis. These were taken from a range of published literature. The key values used to estimate weight change were taken from a study by Bagust et al which was used in the previous dapagliflozin submission for dual therapy. A value of ±0.0061 was applied for each unit increase/decrease in BMI. Utility decrements relating to adverse events were also included in the model.

Costs included in the analysis were drug acquisition costs, adverse event costs and monitoring costs. Drug acquisition costs for the DPP-4 inhibitors were based on a weighted average of sitagliptin, vildagliptin, saxaglitpin and linagliptin, using the company's own market share data. Severe hypoglycaemic event costs as well as the costs of fatal and non-fatal micro-vascular and macro-vascular event complications were included in the analysis Patient monitoring costs, including those related to renal monitoring were applied to both arms as this is considered to be part of the clinical management of type 2 diabetes. Additional monitoring costs were assumed to apply for the initiation of dapagliflozin treatment.

The base case cost per quality-adjusted life year (QALY) was estimated at £10,995 based on an incremental cost of £253 and a QALY gain of 0.023. It should be noted that the base case result for dapagliflozin is driven by weight changes rather than changes in other short term outcomes such as HbA1c and SBP. A range of sensitivity analyses were provided, including one-way, scenario and multivariate sensitivity analysis. Results appeared most sensitive to a reduced time horizon of 20 years, causing the incremental cost-effectiveness ratio (ICER) to increase to £16,250 per QALY. Of particular importance is the sensitivity analysis which assumed weight convergence when patients

moved to the next line of treatment, which increased the ICER to £15,959 per QALY.

The following weaknesses were noted

- The base case result does not incorporate the assumption of weight convergence over time. In the previous submission for dual therapy the company was asked by SMC to provide the results assuming weight convergence as this was considered to be a more realistic assumption in the previous submission for dual therapy. As noted above, when weight convergence was included this resulted in the ICER increasing to £15,959 per QALY.
- Additional analysis was requested from the company in order to test the combined effect of a shorter time horizon (20 years) and including the assumption of weight convergence at second treatment switch. This resulted in the ICER increasing to £23,274 per QALY.
- The results of the NMA appear to be affected by heterogeneity. This may introduce some uncertainty into the results.

Despite these concerns, however, the economic case has been demonstrated.

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

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, which is a U.K. registered charity.
- Diabetes UK Scotland has received funding from several pharmaceutical companies in the past two years.
- Diabetes is a complex and progressive condition which can result in poly pharmacy and consequently poor compliance with treatment. Poorly controlled diabetes can lead to complications such as blindness, amputation, renal disease and reduced life expectancy due often to coronary heart disease and stroke. Poorly controlled diabetes can also affect a patients' ability to meet work commitments.
- Current treatments for type 2 diabetes can cause side effects such as hypoglycaemia, gastric disturbances and weight gain.
- Dapagliflozin is a simple to use once a day medication and may offer an important additional option with the potential to improve weight and glucose control together with delaying progression to insulin therapy.

Additional information: guidelines and protocols

In March 2010 the Scottish Intercollegiate Guidelines Network (SIGN) published clinical guideline number 116, management of diabetes. This recommends that metformin should be considered as the first line oral treatment option for overweight patients with type 2 diabetes. Sulphonylureas should be considered as first line oral agents in patients who are not overweight, who are intolerant of, or have contraindications to, metformin. Pioglitazone can be added to metformin and sulphonylurea therapy, or substituted for either in cases of intolerance. DPP-4 inhibitors may be used to improve blood

glucose control in people with type 2 diabetes. GLP-1 agonists (exenatide or liraglutide) may be used to improve glycaemic control in obese adults (BMI ≥30kg/m^2) with type 2 diabetes who are already prescribed metformin and/or sulphonylureas. A GLP-1 agonist will usually be added as a third line agent in those who do not reach target glycaemia on dual therapy with metformin and sulphonylurea (as an alternative to adding insulin therapy). Liraglutide may be used as a third line agent to further improve glycaemic control in obese adults (BMI ≥30kg/m^2) with type 2 diabetes who are already prescribed metformin and a thiazolidinedione and who do not reach target glycaemia. Careful judgement must be applied in relation to people with long duration of type 2 diabetes on established oral glucose-lowering drugs with poor glycaemic control (>10 years, these individuals being poorly represented in published studies) to ensure insulin therapy is not delayed inappropriately for the perceived benefits of GLP-1 agonists. Third-line options (DPP-4 inhibitors, pioglitazone and GLP-1 agonists) should be continued if personalised HbA1c targets are met, or a reduction in HbA1c of at least 0.5% (5.5mmol/mol) is achieved within three to six months.[12]

Additional information: comparators

The other medicines that could be added to metformin and sulphonylurea include the DPP-4 inhibitors, linagliptin, saxagliptin, sitagliptin and vildagliptin; the GLP-1 agonists, exenatide, liraglutide and lixisenatide; and the thiazolidinedione, pioglitazone. The submitting company has requested that SMC consider dapagliflozin as an alternative to DPP-4 inhibitors only.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Dapagliflozin	**10mg once daily**	**476**
Linagliptin	5mg once daily	432
Sitagliptin	100mg once daily	432
Vildagliptin	50mg twice daily	413
Saxagliptin	5mg once daily	411

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 19 March 2014.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 10,640 in all years. Based on an estimated uptake rate of 3.73% in year 1 rising to 25.74% in year 5, the impact on the gross medicines budget was estimated at £198k in year 1 rising to £1.3m in year 5. As other drugs were assumed to be displaced, the net medicines budget was estimated at £20k in year 1 and £141k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Bristol-Myers Squibb / AstraZeneca. Summary of product characteristics for dapagliflozin (Forxiga)
2. Scottish Medicines Consortium. Advice for dapagliflozin (initial submission), December 2012
3. Scottish Medicines Consortium. Advice for dapagliflozin (resubmission), February 2014
4. *Commercial In Confidence*
5. Matthaei S Rohwedder K, Grohl A , Johnsson E. Dapagliflozin improves glycaemic control and reduces body weight as add-on therapy to metformin and sulphonylurea. Presented at European Association for the Study of Diabetes (EASD) annual meeting, September 2013
6. Evaluation of safety and efficacy of dapagliflozin in subjects with type 2 diabetes who have inadequate glycaemic control on background combination of metformin and sulfonylurea. (NCT01392677). www.clinicaltrials.gov (Last updated 11 February 2014).
7. Cefalu WT Leiter LA, de Bruin TWA et al. Dapagliflozin treatment for type 2 diabetes mellitus patients with comorbid cardiovascular disease and hypertension. Presented at American Diabetes Association meeting, Philadephia 8 to 12 June 20129.
8. Efficacy and safety in patients with type 2 diabetes mellitus, cardiovascular disease and hypertension (NCT01031680). www.clinicaltrials.gov (Last updated 24 September 2013).
9. Leiter LA Cefalu WT, de Bruin TWA et al. Efficacy and safety of dapagliflozin for type 2 diabetes. mellitus patients with a history of cardiovascular disease. Presented at American Diabetes Association meeting, Philadephia 8 to 12 June 2012
10. Efficacy and safety in patients with type 2 diabetes mellitus and cardiovascular disease. (NCT01042977). www.clinicaltrials.gov (Last updated 18 December 2013).
11. Jabbour S, Hardy E, de Bruin TW et al. Dapagliflozin helps reduce HbA1c and body weight in patients with type 2 diabetes as part of triple combination therapy: a subanalysis of 4 clinical studies. Presented at European Association for the Study of Diabetes meeting, Barcelona 23 to 27 September 2013
12. Scottish Intercollegiate Guidelines Network (SIGN) clinical guideline number 116, management of diabetes March 2010.

This assessment is based on data submitted by the applicant company up to and including 16 May 2014.

**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. 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.