



Dapagliflozin in triple therapy for treating type 2 diabetes

Technology appraisal guidance Published: 23 November 2016

www.nice.org.uk/guidance/ta418

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should <u>assess and reduce the environmental</u> impact of implementing NICE recommendations wherever possible.

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This guidance partially replaces TA288.

1 Recommendations

- Dapagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in adults, only in combination with metformin and a sulfonylurea.
- This guidance is not intended to affect the position of patients whose treatment with dapagliflozin in other triple therapy regimens was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Dapagliflozin (Forxiga, AstraZeneca) is a selective sodium–glucose cotransporter 2 (SGLT-2) inhibitor, which blocks the reabsorption of glucose in the kidneys and promotes excretion of excess glucose in the urine.
Marketing authorisation	Dapagliflozin has a UK marketing authorisation for treating type 2 diabetes mellitus to improve glycaemic control in adults: • as monotherapy: when diet and exercise alone do not provide adequate glycaemic control in people for whom use of metformin is considered inappropriate due to intolerance or contraindications • 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.
Adverse reactions	The summary of product characteristics lists the following adverse reactions for dapagliflozin: back pain, balanitis, creatinine renal clearance decrease, dizziness, dysuria, dyslipidaemia, elevated haematocrit, polyuria, urinary tract and genital infection, and vulvovaginitis. Dapagliflozin is not recommended for people with moderate to severe renal impairment (people with a creatinine clearance rate of less than 60 ml/min or an estimated glomerular filtration rate [eGFR] of less than 60 ml/min/1.73 m²). For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	The recommended dosage is 10 mg dapagliflozin orally once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin.
Price	The list price of dapagliflozin is £36.59 for a 28-tablet pack of 5-mg or 10-mg tablets (excluding VAT; 'British national formulary' [BNF], accessed online August 2016). Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

The appraisal committee (<u>section 6</u>) considered evidence submitted by AstraZeneca and a review of this submission by the evidence review group (ERG). See the <u>committee papers</u> for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of dapagliflozin, having considered evidence on the nature of type 2 diabetes and the value placed on the benefits of dapagliflozin by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Patient experience

4.1 The patient expert described the benefits of treatment with dapagliflozin, which she took in addition to 3 other oral agents for diabetes. She felt that dapagliflozin was effective, and easy and flexible to take, which gave her more confidence in self-managing her disease. Because of this she had a more positive outlook and generally felt less stressed and anxious. As someone with needle-phobia, the patient expert particularly appreciated having an additional oral treatment option to delay progression to injectable treatments such as insulin. And she believed that an added bonus of her treatment with dapagliflozin is that it had reduced her blood pressure, meaning she did not have to add a blood pressure medication to her treatment regimen. The clinical experts confirmed that in addition to lowering haemoglobin A1c (HbA1c - a measure of blood glucose levels over the previous 2 to 3 months), selective sodium-glucose cotransporter 2 (SGLT-2) inhibitors such as dapagliflozin have the added benefit of helping to reduce blood pressure. Another significant and characteristic benefit of the SGLT-2 inhibitors is weight loss. This is a particularly important outcome for people with type 2 diabetes because there is a strong association with excess body weight and some treatments, such as insulin, can result in weight gain. The committee concluded that patients and their clinicians would value an additional effective oral treatment option for type 2 diabetes, particularly if it offered additional benefits such as weight loss and blood-pressure reduction.

Current clinical management of type 2 diabetes

The committee noted that dapagliflozin has a licence, and has been 4.2 previously been appraised by NICE, for both monotherapy (when metformin is contraindicated, recommended in NICE technology appraisal guidance 390) and also as part of combination therapy (NICE technology appraisal quidance 288 recommends dapagliflozin in specific dual therapy regimens, but not as triple therapy because of a lack of evidence at the time). This appraisal is a part review of TA288 focussing on triple therapy. The committee queried where dapagliflozin is used most frequently in the treatment pathway. It heard from the clinical experts that there is no consensus about where dapagliflozin would be most appropriate, but the most likely position is probably as dual therapy in combination with metformin. The committee asked the clinical experts what the most relevant comparators are for dapagliflozin as part of triple therapy, noting that the company had excluded the comparators pioglitazone (citing low use in triple therapy in clinical practice) and injectable treatments (stating that oral treatments are used before injectable treatments). It heard from the clinical experts that they considered both of these exclusions to be appropriate. They stated that although many people are taking pioglitazone, with a large number of annual prescriptions as highlighted by the evidence review group (ERG), this is not representative of the number of people being newly prescribed pioglitazone, which is decreasing year on year. The clinical experts stated that this decrease is probably related to concerns about the adverse effects of rosiglitazone (a drug in the same class as pioglitazone that was withdrawn from clinical use because of an increased risk of cardiovascular disorders) and because pioglitazone is associated with an increased risk of oedema and weight gain. When given a choice of treatments, patients almost always prefer a treatment such as dapagliflozin that is associated with weight loss, rather than one that is weight-neutral or causes weight gain. Also, for the population in the scope, the clinical experts stated that a third oral treatment is almost always preferable to an injectable treatment such as insulin. The committee concluded that the comparators included by the company, dipeptidyl peptidase-4 (DPP-4) inhibitors and other SGLT-2 inhibitors, were appropriate for its decision-making.

Clinical effectiveness

Population

4.3 The committee noted that the population in the scope included people with type 2 diabetes that is not controlled on dual therapy with metformin and a sulfonylurea, or with metformin and a DPP-4 inhibitor. However, the company had only presented evidence for the former population because of a lack of evidence for the latter population, and also because it considered that metformin plus a sulfonylurea is the most commonly used regimen. The clinical experts stated that they agreed with the company that the majority of people on dual therapy, who would be eligible for dapagliflozin as a third treatment, would be taking a combination of metformin and a sulfonylurea. The committee concluded that the company had used the most relevant population in its analyses.

Clinical evidence

4.4 The committee was aware that the clinical trial evidence had demonstrated that dapagliflozin in triple therapy is more effective than placebo in reducing HbA1c and weight. In comparison with the other SGLT-2 inhibitors and the DPP-4 inhibitors, the company's network metaanalyses demonstrated that dapagliflozin had a similar effect on HbA1c as the other SGLT-2 inhibitors and DPP-4 inhibitors, but that the SGLT-2 inhibitors produced more weight loss than the DPP-4 inhibitors. The committee heard from the clinical experts that although there are subtle pharmacological differences between the individual SGLT-2 inhibitors, they can generally be considered as a class in terms of effectiveness. Patients with diabetes that does not respond to one SGLT-2 inhibitor will probably not respond to another. However, in some instances, clinicians may prescribe the higher dose of canagliflozin (300 mg) because this is the only SGLT-2 inhibitor that also has an effect on the SGLT-1 mechanism. The committee concluded that it is reasonable to assume that the SGLT-2 inhibitors have a class effect and, when compared with DPP-4 inhibitors, are similarly effective for HbA1c reduction. However, SGLT-2 inhibitors have the added benefit of weight loss.

4.5 The committee noted that the clinical trial evidence (Study 5) at week 8 had also shown a statistically significant reduction in blood pressure when dapagliflozin was compared with placebo, but this was no longer apparent at week 52. However, it heard from the company, the ERG and the clinical experts that the result at week 52 was anomalous, and the company stated that in several other trials the effect on blood pressure had been maintained. The committee concluded that based on this consistent feedback, it is reasonably likely that dapagliflozin also has a sustained beneficial effect on blood pressure.

Adverse effects of treatment

4.6 The patient expert stated that she had not experienced any adverse effects of treatment with dapagliflozin. She noted that she had been advised to drink plenty of water, which she believed had probably helped reduce the risk of an adverse event. The committee was also aware that dapagliflozin is currently already used in clinical practice. It concluded that based on the currently available clinical evidence, dapagliflozin has an acceptable adverse event profile.

Cost effectiveness

Model structure

The committee was aware that the ERG had raised concerns about the transparency of the model used by the company. However, it was also aware that the model had been accepted as appropriate for decision making in previous NICE technology appraisals for type 2 diabetes. The committee noted that the ERG had disagreed with several parameter assumptions used in the company's model, such as the use of values from the network meta-analysis which did not match the clinical trial results. It had presented an alternative base case with several updated assumptions, including the equations used to inform the incidence of complications (section 4.9) and costs related to the duration of treatment (section 4.10). The committee concluded that the model structure was appropriate for decision making.

Health-related quality of life

4.8 The committee was aware that dapagliflozin is effective in reducing HbA1c but also has other beneficial effects, including reduction in weight and systolic blood pressure. It asked the company and the ERG whether these additional benefits had been fully captured in the model. It heard from the ERG that the company had assumed that weight loss was only maintained for 1 year, which was a pessimistic assumption because there is evidence that it lasts for longer. Therefore the model had not adequately captured the quality of life gain associated with weight loss. The clinical experts stated that weight reduction was a sustained effect, alongside the reduction in HbA1c. In addition, the committee heard from the company and the ERG that it was plausible that SGLT-2 inhibitors have an effect on reducing the risk of heart failure. If this is the case, then the model had not captured this health benefit. The committee concluded that the company and the ERG's base cases had not fully captured the health-related quality of life benefits of dapagliflozin.

Clinical effectiveness and cost assumptions

4.9 The committee noted that the company had used older UK prospective diabetes study equations (UKPDS 68) to predict the incidence of diabetes-related complications in the model. However, it heard from the ERG that newer equations are available (UKPDS 82), and these should have been used because they are more up to date. The ERG explained that the newer UKPDS 82 equations predict a lower incidence of diabetes-related myocardial infarction, renal failure and death, and that the use of the older UKPDS 68 equations in the company's costeffectiveness analysis was beneficial for dapagliflozin. In particular, the committee noted that the main differences in modelled costs between dapagliflozin and DPP-4 inhibitors in the company's base case were differences related to the incidence of nephropathy. This was because the company assumed that dapagliflozin has a protective effect on renal function, and also because the older UKPDS 68 equations predict a higher incidence of renal failure than the newer UKPDS 82 equations. The committee heard from the clinical experts that they consider that dapagliflozin has a protective effect on renal function. The committee concluded that it was reasonable for the model to assume a protective

effect of dapagliflozin on renal function, however the use of the older UKPDS 68 equations was questionable.

Treatment costs

The committee noted that when intensifying treatment to insulin in the model, the company assumed that oral therapies were stopped, whereas the ERG, based on expert clinical opinion, assumed that they continued. The clinical experts stated that drugs such as sulfonylureas may be stopped because of a risk of hypoglycaemia, but SGLT-2 inhibitors would probably be continued. The committee concluded that the assumption in the ERG base case that oral treatments continued when intensifying to insulin is a more accurate reflection of NHS practice than the assumption used in the company model.

Most plausible incremental cost-effectiveness ratio (ICER)

- Inhibitors, the company model predicted that dapagliflozin with DPP-4 inhibitors, the company model predicted that dapagliflozin would dominate (that is, would be cheaper and more effective than) DPP-4 inhibitors, whereas the ERG base case for dapagliflozin was £37,997 per quality-adjusted life year (QALY) gained. However the committee noted that both estimates were based on very small differences in the costs and in the QALY gains between dapagliflozin and the DPP-4 inhibitors, and therefore the cost-effectiveness estimates were unstable. The committee also noted that neither base case had taken into account all the health-related quality of life benefits of dapagliflozin (see section 4.8), particularly in relation to weight loss as noted by the ERG. It therefore considered the higher ICER to be an overestimate.
- The committee was aware that there were no discernible differences in costs and effectiveness between the different SGLT-2 inhibitors, 2 of which are already recommended in triple therapy. It was also aware that individualised care is critical in diabetes management (as recommended in NICE's guideline on type 2 diabetes in adults). The committee agreed that it should be up to patients and their clinicians to decide which SGLT-2 inhibitor is most appropriate for them. The committee concluded that dapagliflozin as part of triple therapy in combination with metformin

and a sulfonylurea for type 2 diabetes can be recommended as a costeffective use of NHS resources.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

	Appraisal title: Dapagliflozin in triple therapy for treating type 2 diabetes	Section
Key conclusion		

When comparing dapagliflozin with dipeptidyl peptidase-4 (DPP-4) inhibitors, the company model predicted that dapagliflozin would dominate (that is, would be cheaper and more effective than) DPP-4 inhibitors, whereas the evidence review group (ERG) base case for dapagliflozin was £37,997 per quality-adjusted life year (QALY) gained. However the committee noted that both estimates were based on very small differences in costs and QALYs, and therefore the cost-effectiveness estimates were unstable. The committee also noted that neither base case had taken into account all the health-related quality of life benefits of dapagliflozin. It therefore considered the higher incremental cost-effectiveness ratio (ICER) to be an overestimate. The committee was aware that there were no discernible differences in costs and effectiveness between the different selective sodium-glucose cotransporter 2 (SGLT-2) inhibitors, 2 of which are already recommended in triple therapy. It was also aware that individualised care is critical in diabetes management. The committee agreed that it should be up to patients and their clinicians to decide which SGLT-2 inhibitor is most appropriate for them. The committee concluded that dapagliflozin as part of triple therapy in combination with metformin and a sulfonylurea for type 2 diabetes can be recommended as a cost-effective use of NHS resources.

1.1, 4.8, 4.11, 4.12

Current practice

Clinical need of patients, including the availability of alternative treatments

The patient expert felt that dapagliflozin was effective and easy and flexible to take, which gave her more confidence in self-managing her disease. As someone with needle-phobia, the patient expert particularly appreciated having an additional oral treatment option to delay progression to injectable treatments such as insulin. And she believed that an added bonus of her treatment with dapagliflozin is that it had reduced her blood pressure, meaning she did not have to add a blood pressure medication to her treatment regimen.

4.1

The technology

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The clinical experts stated that in addition to lowering haemoglobin A1c (HbA1c), SGLT-2 inhibitors such as dapagliflozin have the added benefit of helping to reduce blood pressure. Another very significant and characteristic benefit of the SGLT-2 inhibitors is weight loss. This is a particularly important outcome for people with type 2 diabetes because there is a strong association with excess body weight and some treatments, such as insulin, can result in weight gain.	4.1
What is the position of the treatment in the pathway of care for the condition?	Dapagliflozin has a licence for monotherapy (when metformin is contraindicated) and also as part of combination therapy. The clinical experts stated that there is no consensus about where in the treatment pathway dapagliflozin would be most appropriate, but the most common position is probably as dual therapy in combination with metformin. For triple therapy, the comparators pioglitazone and injectable treatments were excluded by the company. The clinical experts considered both of these exclusions to be appropriate because the number of people being newly prescribed pioglitazone is decreasing year on year, and a third oral treatment is almost always preferable to an injectable treatment.	4.2
Adverse reactions	The patient expert stated that she had not experienced any adverse effects of treatment with dapagliflozin. The committee was also aware that dapagliflozin is currently already used in clinical practice. The committee concluded that based on the currently available clinical evidence, dapagliflozin has an acceptable adverse event profile.	4.6
Evidence for clinica	al effectiveness	
Availability, nature and quality of evidence	The clinical evidence included a trial (Study 5) and network meta-analyses.	4.4, 4.5

Relevance to general clinical practice in the NHS	For triple therapy, the comparators pioglitazone and injectable treatments were excluded by the company. The clinical experts considered both of these exclusions to be appropriate because the number of people being newly prescribed pioglitazone is decreasing year on year, and a third oral treatment is almost always preferable to an injectable treatment. The committee concluded that the comparators included by the company, dipeptidyl peptidase-4 (DPP-4) inhibitors and other SGLT-2 inhibitors, were appropriate for its decision-making. The population in the scope included people with type 2 diabetes that is not controlled on dual therapy with metformin and a sulfonylurea, or with metformin and a DPP-4 inhibitor. However, the company had only presented evidence for the former population because of a lack of evidence for the latter population, and also because it considered that metformin plus a sulfonylurea is the most commonly used regimen. The clinical experts stated that they agreed with the company. The committee concluded that the company had used the most relevant population in its analyses.	4.2, 4.3
Uncertainties generated by the evidence	The company did not include all comparators or populations set out in the scope. However the clinical experts stated that the exclusions were appropriate, and the committee accepted the submitted population and comparators as appropriate for decision making. The Study 5 trial at week 8 had shown a statistically significant reduction in blood pressure when dapagliflozin was compared with placebo, but this was no longer apparent at week 52. However the company, the ERG and the clinical experts stated that the week 52 result was anomalous. The committee concluded that based on this consistent feedback, it is reasonably likely that dapagliflozin has a sustained beneficial effect on blood pressure.	4.2, 4.3, 4.5

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Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Not applicable.	_
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The clinical trial evidence demonstrated that dapagliflozin in triple therapy is more effective than placebo for reducing HbA1c and weight. In comparison with the other SGLT-2 inhibitors and the DPP-4 inhibitors, the company network meta-analyses demonstrated that dapagliflozin had a similar effect on HbA1c as the other SGLT-2 inhibitors and DPP-4 inhibitors, but that the SGLT-2 inhibitors produced more weight loss than the DPP-4 inhibitors. Week 8 blood pressure in the Study 5 trial had shown a statistically significant reduction in the dapagliflozin arm compared with placebo, but this was no longer apparent at week 52. However the committee heard from the company, the ERG and the clinical experts that the week 52 result was anomalous. It concluded that based on this consistent feedback, it is reasonably likely that dapagliflozin has a sustained beneficial effect on blood pressure.	4.4, 4.5
For reviews (except rapid reviews): How has the new clinical evidence that has emerged since the original appraisal (TA288) influenced the current recommendations?	New clinical evidence (the Study 5 trial) is available for dapagliflozin in triple therapy regimens. The company also did new network meta-analyses.	4.4, 4.5

Evidence for cost effectiveness		
Availability and nature of evidence	The ERG had raised concerns about the transparency of the model used by the company. However, the model had been accepted as appropriate for decision making in previous NICE technology appraisals for type 2 diabetes. The committee concluded that the model structure was appropriate for decision making.	4.7
Uncertainties around and plausibility of assumptions and inputs in the economic model	The ERG disagreed with several parameter assumptions used in the company's model and had presented an alternative base case with several updated assumptions. The committee concluded that the use of the older UKPDS 68 equations to inform the incidence of complications in the company model rather than using the more recent UKPDS 82 equations was questionable, and that the assumption in the ERG base case that oral treatments continued when intensifying to insulin is a more accurate reflection of NHS practice than the assumption used in the company model.	4.7, 4.9, 4.10
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee heard from the ERG that the assumption by the company that weight loss was only maintained for 1 year was pessimistic because there is evidence that it lasts for longer. The committee also heard from the company and the ERG that it was plausible that SGLT-2 inhibitors have an effect on reducing the risk of heart failure. The committee concluded that the company and the ERG's base cases had not fully captured the health-related quality of life benefits of dapagliflozin.	4.8

Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable.	_
What are the key drivers of cost effectiveness?	The main differences in modelled costs between dapagliflozin and DPP-4 inhibitors in the company's base case were differences related to the incidence of nephropathy. Cost-effectiveness estimates by both the company and the ERG were based on small cost and QALY differences, making the ICERs unstable.	4.9, 4.11, 4.12
Most likely cost- effectiveness estimate (given as an ICER)	When comparing dapagliflozin with DPP-4 inhibitors, the company model predicted that dapagliflozin would dominate DPP-4 inhibitors, whereas the ERG base case for dapagliflozin was £37,997 per QALY gained. However the committee noted that both estimates were based on very small differences in costs and QALYs, and therefore the cost-effectiveness estimates were unstable. The committee also noted that neither base case had taken into account all the health-related quality of life benefits of dapagliflozin. It therefore considered the higher ICER to be an overestimate.	4.11, 4.12
For reviews (except rapid reviews): How has the new cost- effectiveness evidence that has emerged since the original appraisal (TA288) influenced the current recommendations?	The company submitted a new economic model for dapagliflozin in triple therapy regimens.	4.7

Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	_
End-of-life considerations	Not applicable.	_
Equalities considerations and social value judgements	Not applicable.	_

5 Implementation

- 5.1 Section 7(6) of the National Institute for Health and Care Excellence
 (Constitution and Functions) and the Health and Social Care Information
 Centre (Functions) Regulations 2013 requires clinical commissioning
 groups, NHS England and, with respect to their public health functions,
 local authorities to comply with the recommendations in this appraisal
 within 3 months of its date of publication.
- The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has type 2 diabetes and the doctor responsible for their care thinks that dapagliflozin is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The <u>minutes</u> of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Accreditation

