NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA288; Dapagliflozin for the treatment of type 2 diabetes

This guidance was issued in June 2013.

The review date for this guidance was deferred in January 2015.

1. Recommendation

It is recommended that TA288 is partially updated in relation to the use of dapagliflozin in triple therapy regimens (recommendation 1.3). This partial update will be conducted through the single technology appraisal process.

That we consult on this proposal.

The remaining recommendations will be reconsidered when NICE clinical guideline 87 is superseded by the update that is currently in development.

2. Original remit(s)

To appraise the clinical and cost effectiveness of dapagliflozin within its licensed indication for the treatment of type 2 diabetes.

3. Current guidance

1.1 Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87).

1.2 Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

1.3 Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes, except as part of a clinical trial.

1.4 People currently receiving dapagliflozin in a dual or triple therapy regimen that is not recommended for them in 1.1 or 1.3 should be able to continue treatment until they and their clinician consider it appropriate to stop

4. Rationale[1]

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

At the time TA288 was developed, there were no completed clinical trials of dapagliflozin as a triple therapy add-on to 2 other oral agents. In the absence of direct clinical evidence the Committee concluded that dapagliflozin as triple therapy in combination with metformin and a sulfonylurea should not be recommended for treating type 2 diabetes except as part of the ongoing clinical trials.

There is now one randomised placebo-controlled trial of dapagliflozin in combination with a sulfonylurea and metformin and another comparing saxagliptin plus dapagliflozin, saxagliptin plus placebo, and dapagliflozin plus placebo as add-on therapy to baseline metformin. The recommendation that dapagliflozin triple therapy with metformin and a sulfonylurea should be used only in clinical trials may no longer be relevant.

There was no evidence to suggest that the other recommendations require review, although recommendation 1.1, which refers to clinical guideline 87, will need to be reconsidered when that guideline is superseded. This will be the subject of a separate consultation.

5. Implications for other guidance producing programmes

The Centre for Clinical Practice (CCP) agrees with the proposal to update recommendation 1.3 in TA288 through an STA and to reconsider the other recommendations in TA288 when CCP's update of its type 2 diabetes guideline has been published. This guideline update cross-refers to all the TA guidance on SGLT-2 inhibitors, including TA288.

6. New evidence

The search strategy from the original Evidence Review Group report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from May 2011 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

Background

When technology appraisal guidance 288 was published in June 2013, there was a lack of data on the clinical effectiveness of dapagliflozin as part of triple therapy. The only available data came from a post-hoc analysis of a subset of older patients recruited in 2 trials of dapagliflozin as an add-on to metformin and a sulfonylurea; these patients had type 2 diabetes and cardiovascular disease. During the appraisal, the company noted that the patients in the post hoc analysis were not representative of the triple therapy population. The Committee was aware of the limitations of the clinical-effectiveness data for the triple therapy regimen and concluded that caution should be taken when interpreting the results. The Committee also acknowledged that dapagliflozin dominated the comparator treatments in the company's economic model (that is, resulted in cost savings and better outcomes) but agreed that the cost-effectiveness analyses should be considered as exploratory in nature. The

Committee was aware of an ongoing clinical trial to evaluate dapagliflozin as part of triple therapy (Study 05). Based on the available evidence, the Committee did not recommend dapagliflozin in a triple therapy regimen except as part of the ongoing clinical trial.

New evidence of clinical effectiveness

Study 05 has now been published (Matthaei et al. 2015). This randomised double-blind parallel-group trial recruited people with type 2 diabetes who had inadequate glycaemic control on metformin and a sulfonylurea. Patients were randomly allocated to receive dapagliflozin, metformin and a sulfonylurea (n=109) or placebo, metformin and a sulfonylurea (n=109). The mean reduction in glycated haemoglobin (HbA1c)[2] from baseline to 24 weeks was greater in patients randomised to dapagliflozin (0.86%) than in patients randomised to placebo (0.17%); the difference between groups was statistically significant ($p<0.0001$; see table 5 of the summary of product characteristics). At 24 weeks, the percentage of patients achieving an HbA1c level below 7% was greater in the dapagliflozin group (31.8%) than in the placebo group (11.1%), $p<0.0001$. Patients randomised to dapagliflozin also lost more weight (mean 2.65 kg) than patients randomised to placebo (mean 0.58 kg), although the dapagliflozin group had a greater increase in cholesterol. Adverse events occurred in 48.6% of the dapagliflozin group and 51.4% of the placebo group (Matthaei et al. 2015).

During technology appraisal 288, the discussion of triple therapy focussed on a regimen of dapagliflozin, metformin and a sulfonylurea. Evidence is now available for a regimen of dapagliflozin, metformin and saxagliptin (a dipeptidyl peptidase-4 [DPP-4] inhibitor). Rosenstock et al. (2015) recruited people with type 2 diabetes who had inadequate glycaemic control on metformin. Patients were randomly allocated to one of three groups (Table 1). After 24 weeks, patients allocated to dapagliflozin, metformin and saxagliptin had a greater mean reduction in HbA1c than patients allocated to dual therapy with either dapagliflozin and metformin or saxagliptin and metformin. The regimen of dapagliflozin, metformin and saxagliptin is not referred to in the summary of product characteristics for dapagliflozin, so it is not clear if this combination is within the marketing authorisation.

Table 1. Drug regimens and results for the trial of Rosenstock et al. (2015).

Regimen (n)	**Mean change from baseline in HbA1c after 24 weeks**
Dapagliflozin, metformin and saxagliptin (n=179)	−1.5%
Dapagliflozin, metformin and placebo (n=179)	−1.2%*
Saxagliptin, metformin and placebo (n=176)	−0.9%**
* Significantly different from dapagliflozin, metformin and saxagliptin group; p<0.02. ** Significantly different from dapagliflozin, metformin and saxagliptin group; p<0.0001.	

[2] HbA1c provides a measure of average plasma glucose over the preceding 8 to 12 weeks. A difference of 5 mmol/mol (0.5%) is considered to be clinically important (draft NICE guideline on the management of type 2 diabetes in adults). The target HbA1c level is different for each individual, but is often in the region of 6.5% to 7.0%.

The current review did not find evidence about the clinical effectiveness of dapagliflozin compared with relevant comparators (such as DPP-4 inhibitors) in a triple therapy regimen. Moreover, the review did not find evidence about the cost effectiveness of dapagliflozin in a triple therapy regimen.

Marketing authorisation and price

Based on the results of Study 05, the summary of product characteristics for dapagliflozin was updated in October 2014. Sections 4.8 (undesirable effects) and 5.1 (pharmacodynamic properties) were changed to include information on the efficacy and safety of dapagliflozin in a triple therapy regimen with metformin and a sulfonylurea. There have been no changes to licensed indications for dapagliflozin.

In February 2014, a formulation of dapagliflozin combined with metformin (Xigduo, AstraZeneca) was granted a marketing authorisation. The indications for dapagliflozin and Xigduo are similar and their price is the same.

The price of dapagliflozin has not changed since technology appraisal 288 (British National Formulary May 2015). During technology appraisal 288, the Committee concluded that the main comparator for dapagliflozin was the DPP−4 inhibitors; the price of these drugs has not changed.

Relevant NICE guidance

NICE has published technology appraisals guidance on canagliflozin (TA315) and empagliflozin (TA336) for treating type 2 diabetes. Like dapagliflozin, these drugs are oral selective sodium-glucose cotransporter-2 inhibitors. The relevant part of technology appraisal 315 recommends canagliflozin in a triple therapy regimen for treating type 2 diabetes in combination with either metformin and a sulfonylurea, or metformin and a thiazolidinedione. Technology appraisal 336 made the same recommendation for empagliflozin. Accordingly, canagliflozin and empagliflozin may need to be considered as comparators if technology appraisal 288 is updated.

An update of NICE clinical guidelines 66 and 87 for the management of type 2 diabetes is expected to be published in August 2015. The draft guideline refers to technology appraisal 288 but does not incorporate or update the recommendations.

Conclusion

Two new studies provide evidence about the clinical effectiveness of dapagliflozin in a triple therapy regimen. Study 05 examined dapagliflozin in combination with metformin and a sulfonylurea, whilst Rosenstock et al. (2015) examined dapagliflozin in combination with metformin and saxagliptin. It may be appropriate to conduct a single technology appraisal in order to consider this new evidence and, if necessary, update recommendation 1.3 from technology appraisal 288

8. Equality issues

No issues relating to equality considerations were raised in the original guidance. The Committee concluded that its recommendations would not have a particular

impact on any of the groups whose interests are protected by the equalities legislation and that there was no need to alter or add to its recommendations.

GE paper sign off: Janet Robertson, 2 June 2015

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A review of the appraisal will be planned into the NICE's work programme.	Yes (part review of NICE TA288 rec 1.3).
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	No

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment

- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Canagliflozin in combination therapy for treating type 2 diabetes. Technology appraisals guidance 315. Date issued: June 2014.

Empagliflozin in combination therapy for treating type 2 diabetes. Technology appraisals guidance 336. Date issued: March 2015.

The management of type 2 diabetes. Clinical Guideline CG66. Date issued: May 2008. An update is in progress, with an expected publication date of August 2015.

The management of type 2 diabetes - newer agents (partial update of CG66). Clinical guideline CG87. Date issued: May 2009. An update is in progress, with an expected publication date of August 2015.

Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. NICE Guideline 3. Date issued: February 2015.

Diabetes in adults. Quality Standard QS6. Date issued: March 2011.

Diabetes Pathway. Created May 2011, last updated March 2015.

In progress

Canagliflozin, dapagliflozin and empagliflozin for the monotherapy treatment of type 2 diabetes (ID756). Expected date of publication: May 2016.Diabetes in children and young people: diagnosis and management of type 1 and type 2 diabetes in children and young people. Clinical Guideline. Expected date of publication: August 2015.

(Also see above for updates of already published guidance that are in progress.)

Details of changes to the indications of the technology

Indication considered in original appraisal – TA288	Proposed indication (for this appraisal)
"Dapagliflozin (Forxiga, Bristol-Myers Squibb and AstraZeneca) is a sodium–glucose cotransporter-2 (SGLT-2) inhibitor…It has a UK marketing authorisation '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 with other glucose-lowering agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control'. The subject of this appraisal is the add-on therapy indication."	Unchanged. Source: Dapagliflozin SPC (accessed 20 May 2015).

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Ertugliflozin (Pfizer)	Phase III, [redacted]
Human insulin powder for inhalation (Afrezza, MannKind/Sanofi)	Approved by the FDA in June 2014. [redacted]

Registered and unpublished trials: TA288

Trial name and registration number	Details
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects With Type 2 Diabetes With Inadequately Controlled Hypertension on an Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin Receptor Blocker (ARB) and an Additional Antihypertensive Medication. NCT01195662	Phase III, completed. Enrolment: 2245 Primary completion date: February 2013.
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Therapy With Dapagliflozin Added to Saxagliptin in Combination With Metformin Compared to Therapy With Placebo Added to Saxagliptin in Combination With Metformin in Subjects With Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin and Saxagliptin. NCT01646320	Completed. Estimated enrolment: 280 Primary completion date: August 2014.
Dapagliflozin Effect on Cardiovascular Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes. DECLARE-TIMI58 NCT01730534	Phase III, recruiting. Estimated enrolment: 27000 Primary completion date: April 2019.
Forxiga (Dapagliflozin Propanediol Monohydrate) Prescription Event Monitoring Program. NCT01944618	Phase not given, recruiting. Estimated enrolment: 5000 Primary completion date: December 2014.

Trial name and registration number	Details
A 26-week International, Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3bTrial With a Blinded 26-week Long -Term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered With Dapagliflozin in Combination With Metformin Compared to Sitagliptin in Combination With Metformin in Adult Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone NCT02284893	Phase III, recruiting. Estimated enrolment: 420 Primary completion date: September 2016.
A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase III Study to Evaluate the Glycemic Efficacy and Renal Safety of Dapagliflozin in Patients With Type 2 Diabetes Mellitus and Moderate Renal Impairment (CKD 3A) Who Have Inadequate Glycemic Control NCT02413398	Phase III, not yet recruiting. Estimated enrolment: 302 Primary completion date: February 2017.
Therapeutic Efficacy and Safety of Sitagliptin, Dapagliflozin and Lobeglitazone in Patients With Type 2 Diabetes Mellitus Inadequately Controlled on Glimepiride and Metformin. NCT02338921	Phase IV, not yet recruiting. Estimated enrolment: 78 Primary completion date: September 2017
A 52-week International, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3bTrial With a Blinded 104-week Long -Term Extension Period to Evaluate the Efficacy and Safety of Saxagliptin Co-administered With Dapagliflozin in Combination With Metformin Compared to Glimepiride in Combination With Metformin in Adult Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Therapy Alone NCT02419612	Phase III, not yet recruiting. Estimated enrolment: 420 Primary completion date: August 2017

Trial name and registration number	Details
Effect of Dapagliflozin on 24-hour Blood Glucose in T2DM Patients Inadequately Controlled With Either Metformin Or Insulin NCT02429258	Phase IV, not yet recruiting. Estimated enrolment: 92 Primary completion date: October 2015
Effect of Saxagliptin in Addition to Dapagliflozin and Metformin on Insulin Resistance, Islet Cell Dysfunction, and Metabolic Control in Subjects with Type 2 Diabetes Mellitus on Previous Metformin Treatment EUCTR2014-003788-39-DE	Date of first enrolment: 17/12/2014

Relevant services covered by NHS England specialised commissioning

NHS England has commissioned specialised insulin-resistant diabetes services (all ages). The specific therapies referred to are leptin, recombinant human insulin-like growth factor (rhIGF1), U500 insulin, immunosuppression therapy, GPL-1 agonists (liraglutide, exenatide).

References

European Medicines Agency (2015). Dapagliflozin: Summary of product characteristics. Accessed 20 May 2015: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002322/human_med_001546.jsp&mid=WC0b01ac058001d124

Matthaei S, Bowering K, Rohwedder K et al. (2015) Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care 38 (3): 365-372.

NICE (2015). Draft NICE guideline. Type 2 diabetes in adults: management of type 2 diabetes in adults. Accessed 20 May 2015: http://www.nice.org.uk/guidance/gid-cgwave0612/documents/type-2-diabetes-draft-guideline2

Rosenstock J, Hansen L, Zee P et al. (2015) Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes Care* 38 (3): 376-383.