NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

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

Final recommendation post consultation
TA 288 will be partially updated (recommendation 1.3 only) through the STA process

1. Background

This guidance was issued in June 2013.

At the GE meeting of 23 June 2015 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

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The remaining recommendations will be reconsidered when NICE clinical guideline 87 is superseded by the update that is currently in development.

3. Rationale for selecting this proposal

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.

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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although recommendation 1.1, which refers to clinical guideline 87, will need to be reconsidered when that guideline is superseded.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.

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: Janssen **Response to proposal:** Agree Janssen welcomes the opportunity for a technology recommendation to be re-reviewed within the context of a product's full licence indication upon the release of new evidence. Accordingly, Janssen has no further comments to share at present and looks forward to future engagement during this review process.	**Comment from Technology Appraisals** Thank you for your comments.

Respondent: Boehringer Ingelheim **Response to proposal:** No comment	**Comment from Technology Appraisals** Thank you for your comments.

Respondent: AstraZeneca **Response to proposal:** Agree AstraZeneca welcomes the recommendation that TA288 is partially updated in relation to the use of dapagliflozin in triple therapy regimens (recommendation 1.3). Further, we agree that this partial update should be conducted through the Single Technology Appraisal process. <u>Rationale:</u> Since TA288 was developed, new evidence has become available, which should be considered in the partial update: • Randomised controlled trials of the efficacy of dapagliflozin in triple therapy regimens (study 5 in combination with sulphonylurea and metformin; and study 10 in combination with a DPP-4 inhibiitor and metformin) for patients failing to achieve glycaemic control with dual regimens (metformin + sulphonylurea/metformin + DPP-4 inhibitor) (see section 5.1 of the dapagliflozin SmPC) • [redacted] • Cost effectiveness evidence demonstrating that dapagliflozin is cost effective in a triple therapy regimen with a sulphonylurea and metformin, as compared to a triple regimen with a DPP-4 inhibitor, a sulphonylurea and metformin. A brief summary of the evidence is provided below. We agree that there is no new evidence to suggest that the other TA288 recommendations require review. **<u>New evidence of clinical effectiveness</u>** ***Dapagliflozin in combination with a sulphonylurea and metformin*** As described in the review proposal document from NICE, the results of the pivotal phase III	**Comment from Technology Appraisals** Thank you for your comments. If this topic is referred for appraisal, please include the relevant evidence in your submission to NICE.

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study (Study 5) supporting the use of dapagliflozin in a triple therapy regimen have now been published (Matthaei et al, 2015). Study 5 was a 24-week, international, multi-centre, randomised, double-blind, parallel-group, placebo-controlled study with a 28-week subject blinded extension period which evaluated the efficacy and safety of dapagliflozin 10 mg daily in subjects with type 2 diabetes who were inadequately controlled on metformin and a sulphonylurea. At week 24, dapagliflozin in combination with metformin and a sulphonylurea resulted in significant and clinically relevant benefits as regards HbA1c and weight, as well as fasting plasma glucose and systolic blood pressure, compared with placebo with benefits sustained to 52 weeks. ***Dapagliflozin in combination with a DPP-4 inhibitor (sitagliptin) and metformin*** Study 10 (Jabbour et al, 2014) is a phase III, 24-week, placebo-controlled randomised trial which included two pre-specified strata (groups) of patients failing to achieve glycaemic control with: Stratum 1: DPP4 (sitagliptin) monotherapy Stratum 2: DPP4 (sitagliptin) + metformin Key stratum 2 results were as follows: • When added to sitagliptin plus metformin, dapagliflozin significantly decreased HbA1c compared with placebo • Statistically significant improvements were observed with dapagliflozin versus placebo for change in total body weight As regards the specific query in the NICE review proposal document regarding the dapagliflozin marketing authorisation, it should be noted that the regimen of dapagliflozin in combination with a DPP-4 inhibitor and metformin is licensed for patients with inadequate control on dual therapy (DPP-4 inhibitor + metformin) (see Table 4 in the dapagliflozin SmPC). Study 169 (Rosenstock et al, 2015), described in the NICE review proposal document included *patients with inadequate control on metformin monotherapy,* and is not within license.	Comments noted. If this topic is referred for appraisal, NICE will hold a scoping consultation to ensure that the scope includes the relevant treatment combinations and comparators.

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[redacted]

New Cost Effectiveness Evidence

Using the validated CARDIFF diabetes cost-utility model, it has been demonstrated that for patients whose type 2 diabetes is not well controlled on metformin and a sulphonlurea alone, dapagliflozin in combination with metformin and a sulphonylurea is cost-effective compared to the DPP-4 inhibitor class with a base case ICER of under £11,000 per QALY gained (Charokopou et al, 2014).

References

Charokopou M.H., Eddowes L.A., Griffiths M., Verheggen B.G., Gabriel Z., Tolley K. Cost-effectiveness of dapagliflozin compared to DPP-4 inhibitors as triple therapy in combination with metformin and a sulphonylurea in the treatment of type 2 diabetes mellitus from a UK healthcare perspective. Poster presented at ISPOR 17th Annual European Congress 8-12 November 2014, Amsterdam, The Netherlands

Jabbour A S, Hardy E, Sugg J, Parikh S,2 for the Study 10 Group. Dapagliflozin Is Effective as Add-on Therapy to Sitagliptin With or Without Metformin: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. Diabetes Care Volume 37, March 2014.

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

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Respondent: Association of British Clinical Diabetologists **Response to proposal:** Agree ABCD would like to support that update. Should the guidance (TA 288) be updated based on the availability of any new evidence. ABCD also believes that it would be logical to incorporate more detail about the place of this class of drugs in the management of adults with type 2 diabetes in the update of the Type 2 Guidelines (consultation for which closed on Friday 24/7/2015). [sic] The Royal College of Physicians endorsed the response from the Association of British Clinical Diabetologists.	**Comment from Technology Appraisals** Thank you for your comments. If this topic is referred for appraisal, the Committee will discuss the appropriate place for this technology in the treatment pathway.

Respondent: Merck Sharp & Dohme **Response to proposal:** Agree As discussed within the proposed scope document, NICE are recommending a partial update of TA288 for dapagliflozin (section 1.3), relevant to dapagliflozin in triple therapy. This will consider recently published evidence for dapagliflozin in combination with metformin plus a sulfonylurea (Matthaei et al. 2015), and dapagliflozin in combination with saxagliptin (Rosenstock et al. 2015). In addition to the studies, as detailed above, there have been safety letters issued by the three manufacturers of the SGLT-2s to healthcare professionals regarding diabetic ketoacidosis.[1] The EMA, on the 12th June, confirmed an investigation into the SGLT-2 class to determine the risk of diabetic ketoacidosis. Will this evidence be included in the STA review process? The remit of the proposal of TA288 does not include dual therapy. MSD understand that there is a limited potential for a MTA, inclusive of TA315 and TA336 due to their recent publication. However, it is possible to consider a review of the dual therapy recommendations of dapagliflozin (TA288) in section 1.1 using the same STA process. The	**Comment from Technology Appraisals** Thank you for your comments.

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rationale for this request:

- Discrepancy exists between the use of dapagliflozin (TA288), canagliflozin (TA315) and empagliflozin (TA336) at dual therapy when used in combination with metformin.
- The anticipated publication of the clinical guideline for patients with type 2 diabetes (CG87). It is likely that the existing recommendation for dapagliflozin (section 1.1), which recommends the use of dapagliflozin "only if it used as described for a dipeptidyl peptidase inhibitor (DDP-4 inhibitor) in the type2 diabetes (NICE clinical guideline 87)"[2] will be unsubstantiated based on the evidence considered within the updated clinical guideline for the DPP-4 inhibitor class.

Therefore, it would seem logical to either amend the recommendation of dapagliflozin to reflect both canagliflozin and empagliflozin, or schedule a review of dual therapy within the same STA process. This would also preserve longevity of the final TA document and the applicability of such recommendations to clinical practice.

In section seven "marketing authorisation and price" the NICE committee stated that the main comparator for dapagliflozin was the DPP-4 inhibitor class. However, since the publication of TA288 both canagliflozin and empagliflozin have received positive TA recommendations. The manufacturer of canagliflozin presented comparator treatments inclusive of a; DPP-4 inhibitor, sulfonylurea, thiazolidinediones, GLP-1 analogues, dapagliflozin, and insulin.[3] Similarly, the manufacturer of empagliflozin presented comparator evidence for the DPP-4 inhibitors and other SGLT-2s (canagliflozin and dapagliflozin), which was accepted by the committee.[4] Therefore, these technologies should be recognised as suitable comparators and included in any analyses moving forward.

References

1. EMA, SGLT2 inhibitors Article-20 procedure - Review started; published 12th June 2015; date accessed, 23rd July 2015 http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors__20/Procedure_started/WC500187926.pdf
2. NICE, Dapagliflozin in combination therapy for treating type 2 diabetes (TA288); Issued June 2013; accessed, 23rd July 2015 http://www.nice.org.uk/guidance/ta288/resources/guidance-dapagliflozin-in-combination-therapy-for-treating-type2-diabetes-pdf
3. NICE, Canagliflozin in combination therapy for treating type 2 diabetes (TA315); Issued June 2014; accessed, 23rd July 2015, http://www.nice.org.uk/guidance/ta315/resources/guidance-canagliflozin-in-combination-therapy-for-treating-type2-diabetes-pdf

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4. NICE, Empagliflozin in combination therapy for treating type 2 diabetes (TA336); Issued March 2015; accessed, 23rd July 2015 http://www.nice.org.uk/guidance/ta336/resources/guidance-empagliflozin-in-combination-therapy-for-treating-type2diabetes-pdf	

Paper signed off by: Janet Robertson, 19 August 2015

Contributors to this paper:

Technical Lead: Rosie Lovett

Project Manager: Andrew Kenyon

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