NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA336; Empagliflozin in combination therapy for treating type 2 diabetes

Original publication date:	March 2015
Review date	March 2018
Existing recommendations:	Optimised To see the complete existing recommendations and the original remit for TA336, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

Empagliflozin was recommended in 2015 as an optimised recommendation in-line with guidance produced for its key comparators. The committee considered this appropriate as the incremental differences between the costs and QALYs for empagliflozin and its key comparators canagliflozin, dapagliflozin and sitagliptin were small, and it concluded that empagliflozin should be recommended as an option for the same populations. There has been no new comparative evidence identified which would change this recommendation and TA315, the related guidance for canagliflozin in combination therapy, was moved to the static list in October 2017.

EMPA-REG, a large randomised controlled study, was identified and investigates empagliflozin compared with placebo on cardiovascular morbidity and mortality in people with type 2 diabetes at high risk for cardiovascular events who were receiving standard care[1-3]. People with type 2 diabetes at high risk for cardiovascular events are a subgroup of the population covered by the recommendation in TA336. The results of this trial showed a showed a significant reduction in cardiovascular and all-cause mortality. One study investigated the cost-utility of empagliflozin for a UK population based on the results of the EMPA-REG trial[4]. This study predicts empagliflozin has an incremental cost effectiveness ratio of £4,365 per QALY gained compared with standard of care. These results are unlikely to change the optimised recommendation for the full population.

One meta-analysis was identified which investigated cardiovascular outcomes of empagliflozin compared to placebo[5]. This study included studies which recruited

people of low risk for cardiovascular events. The results are consistent with the EMPA-REG trial.

The committee was also concerned that the lack of long-term follow-up data meant that there was uncertainty about the adverse-event profile of empagliflozin. Since the guidance was published, a number of safety issues have arisen. For example the Medicines and Healthcare products Regulatory Agency (MHRA) published a drug safety update for SGLT-2 inhibitors in 2017. The drug safety update was about canagliflozin, which may increase the risk of lower-limb amputation (mainly toes) in patients with type 2 diabetes. Although there was no evidence of an increased risk for empagliflozin, the MHRA warned about a possible class effect. The EMPA-REG trial did not report lower-limb amputations. The EMPA-REG study did not report any long-term safety issues which would lead to changes in the original guidance.

Overall, since TA336 was published, new data has emerged suggesting that empagliflozin may be effective in reducing cardiovascular events for people with type 2 diabetes at high risk for cardiovascular events. Some safety issues have been highlighted by regulators in Europe and the US for a related technology. This new evidence is unlikely to lead to changes in the recommendations in the original guidance.

3. Summary of new evidence and implications for review

Has there been any change to the price of the technology since the guidance was published?
No
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
The marketing authorisation for empagliflozin has changed. In the original guidance it was indicated for: 'the treatment of type 2 diabetes mellitus to improve glycaemic control in adults - 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 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'. In 2017 the indication was amended to: 'the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: - as monotherapy when metformin is considered inappropriate due to intolerance

- in addition to other medicinal products for the treatment of diabetes' The change to the marketing authorisation does not have a material impact on the existing guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
Key uncertainty in TA315 related to the lack of long-term follow-up data. Evidence identified from the 8-year EMPA-REG study suggests that empagliflozin can reduce cardiovascular events in a high risk population. The EMPA-REG study did not report any outcomes or long-term safety issues which would lead to changes in the original guidance.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.

The search strategy from the original ERG was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January, 2014 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 above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

No equality issues raised

GE paper sign off: **Meindert Boysen, 01 March 2018**

Contributors to this paper:

Information Specialist: Daniel Tuvey

Technical Analyst: Thomas Strong

Associate Director: Janet Robertson

Project Manager: Emily Richards

Appendix A – Information from existing guidance

5. Original remit

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

6. Current guidance

1.1 Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- a sulfonylurea is contraindicated or not tolerated, or
- the person is at significant risk of hypoglycaemia or its consequences.

1.2 Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:

- metformin and a sulfonylurea or
- metformin and a thiazolidinedione.

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

1.4 People currently receiving treatment initiated within the NHS with empagliflozin that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

The cost of empagliflozin is £36.59 (excluding VAT) per pack of 28 tablets for both 10 mg and 25 mg doses (MIMS December 2014). The annual cost of empagliflozin is estimated to be £477.30.

Appendix B – 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.	No
The decision to review the guidance should be deferred.	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

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	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.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Type 2 diabetes in adults: management (2015 updated 2016) NICE guideline NG28. Partial update in progress – publication date to be confirmed.

Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (2016) NICE technology appraisal guidance 390

In progress

Empagliflozin for reducing the risk of cardiovascular events in type 2 diabetes [ID1037]. Technology appraisal. Publication date: Suspended

Ertugliflozin for treating type 2 diabetes ID1158 Technology appraisal. Publication date: TBC

Referred - QSs and CGs

Diabetes in adults (2011: updated in 2016) NICE quality standard 6

Diabetes in children and young people (2016) NICE quality standard 125

2. Registered and unpublished trials

Trial name and registration number	Details
A 52-week Randomised, Double-blind, Placebo-controlled, Parallel-group, Efficacy and Safety Study of Empagliflozin Once Daily, as an add-on to Insulin in Japanese Patients With Type 2 Diabetes Mellitus With Insufficient Glycaemic Control (NCT02589639)	269 participants Study Start Date: October 28, 2015 Estimated Study Completion Date: January 10, 2018 Active, not recruiting

Trial name and registration number	Details
Efficacy and Safety of Oral Semaglutide Versus Empagliflozin in Subjects With Type 2 Diabetes Mellitus (NCT02863328)	816 participants Study Start Date: August 10, 2016 Estimated Study Completion Date: March 12, 2018 Active, not recruiting
A 26-week Randomized, Double-blind, Controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin Compared to Empagliflozin, and Placebo in Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control on Dipeptidyl Peptidase 4 Inhibitor (DPP4(i)) With or Without Metformin (NCT03351478)	700 participants Actual Study Start Date: November 27, 2017 Estimated Study Completion Date: May 2019 Recruiting
Double Blind Comparison Study of JARDIANCE® (Empagliflozin) in Prehypertensives Type II Diabetics With Metformin (NCT01001962)	1054 participants Study Start Date: January 2016 Estimated Study Completion Date: January 2020 Not yet recruiting

3. Relevant services covered by NHS England specialised commissioning

NHS England (2013) NHS STANDARD CONTRACT FOR INSULIN-RESISTANT DIABETES SERVICES (ALL AGES): PARTICULARS, SCHEDULE 2 – THE SERVICES, A- SERVICE SPECIFICATION (Ref: A03/S(HSS)/b)

4. Additional information

Medicines and Healthcare products Regulatory Agency (MHRA) (2017) SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes)

Appendix D – References

1. Fitchett D, Zinman B, Wanner C, Lachin J M, Hantel S, Salsali A, Johansen O E, Woerle H J, Broedl U C, and Inzucchi S E (2016) Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME trial. Italian Journal of Medicine 10(Supplement 2), 45

2. Zinman Bernard, Inzucchi Silvio E, Lachin John M, Wanner Christoph, Ferrari Roberto, Fitchett David, Bluhmki Erich, Hantel Stefan, Kempthorne-Rawson Joan, Newman Jennifer, Johansen Odd Erik, Woerle Hans-Juergen, and Broedl Uli C (2014) Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOMETM). Cardiovascular diabetology 13, 102

3.Zinman Bernard, Wanner Christoph, Lachin John M, Fitchett David, Bluhmki Erich, Hantel Stefan, Mattheus Michaela, Devins Theresa, Johansen Odd Erik, Woerle Hans J, Broedl Uli C, Inzucchi Silvio E, and Investigators Empa-Reg Outcome (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 373(22), 2117-28

4. Daacke I, Kandaswamy P, Tebboth A, Kansal A, and Reifsnider O (2016) Cost-effectiveness of empagliflozin (jardiance) in the treatment of patients with type 2 diabetes mellitus (T2DM) in the UK based on EMPA-REG outcome data. Value in Health 19(7), A673

5. Salsali A, Kim G, Woerle H J, Broedl U C, and Hantel S (2017) Cardiovascular safety of empagliflozin in patients with Type 2 diabetes: A metaanalysis of placebo-controlled trials. Diabetic Medicine 34(Supplement 1), 32