NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA315; Canagliflozin in combination therapy for treating type 2 diabetes

Original publication date:	June 2014
Review date	May 2017
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA315, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Rationale

The search strategy from the original ERG report for TA315 was adapted and run on the Cochrane Library, Medline, Medline In-Process and Embase. References from August 2013 onwards were reviewed and additional searches of clinical trials registries and other sources were also carried out. Several recent systematic reviews and meta-analyses on the efficacy of canagliflozin were found as part of the systematic literature search (Zhong et al., 2017, Yang et al., 2015, Kuar et al., 2015). These did not report any additional randomised controlled trials meeting the inclusion criteria other than those that were considered in TA315. See Appendix C for further details of ongoing and unpublished studies.

One of the appraisal committee's conclusions was that, as the company had not presented any evidence of the effectiveness of canagliflozin compared with a sulfonylurea, it was unable to make a recommendation on the dual therapy combination of canagliflozin and a sulfonylurea. Since TA315, a substudy of the on-going CANagliflozin cardioVascular Assessment Study (CANVAS) compared canagliflozin (either 100 mg or 300 mg) plus a sulfonylurea with sulfonylurea monotherapy for patients with a history or high risk of cardiovascular disease and inadequate glycaemic control (Fulcher et al., 2015). Although only 127 patients met the eligibility criteria for the substudy, at 18-weeks, canagliflozin as an add-on to a sulfonylurea led to a statistically significant reduction in HbA_{1c}, fasting plasma glucose and body weight (300 mg dose only) compared with sulfonylurea monotherapy. The main weakness of the study is the small sample size, which the authors explain reflects a decrease in the use of sulfonylureas as initial therapy in

general and the small number of people managed on sulfonylurea monotherapy. As the evidence appears to be limited to this small study and the use of sulfonylureas at this stage in the treatment pathway is decreasing, a partial review of TA315 does not seem warranted.

A further uncertainty highlighted by the committee in TA315 was about the long-term efficacy of canagliflozin. In particular, the committee was concerned that there was a lack of evidence to support the company's modelling of HbA_{1c} drift, a key driver of the model. However, the literature search did not find any longer term follow-up studies published since the original guidance was produced.

The committee was also concerned that the lack of long-term follow-up data meant that there was uncertainty about the safety profile of canagliflozin, relating in particular to cardiovascular adverse events. Since the guidance was published, a number of safety issues have arisen. For example, in 2015 the FDA revised the label for canagliflozin to include updates on bone fracture risk and new information on bone mineral density. However, the EMA concluded in 2016 that "the benefits of [sodium–glucose cotransporter-2 inhibitors] continue to outweigh the risks in the treatment of type 2 diabetes". Moreover, a study published in 2017 (Pfeiffer et al.) reported outcomes for 3 cardiovascular markers based on pooled data from 4 randomised controlled trials. Canagliflozin was associated with improvements in all 3 markers compared with placebo, suggesting the canagliflozin is not associated with worse cardiovascular outcomes. The on-going CANVAS study will assess the risk of major cardiovascular events such as cardiovascular death, non-fatal myocardial infarction and stroke. It is due to complete in 2017. A partial update of NICE's clinical guideline on type 2 diabetes in adults is expected to be published in December 2017 and is reviewing the clinical effectiveness of sodium–glucose cotransporter-2 inhibitors on cardiovascular outcomes. A further study, CREDENCE, which is due to complete in 2019, will also report on cardiovascular as well as renal outcomes.

Overall, since TA315 was published, some new data has emerged suggesting that canagliflozin may be effective as an add-on therapy to a sulfonylurea, but this was based on a small sample of patients, and use of sulfonylureas at this stage of the treatment pathway is declining in clinical practice. Some safety issues have been highlighted by regulators in Europe and the US but they have concluded that the benefits of canagliflozin continue to outweigh the risks. 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?
Since the guidance has been published, the price of the 300 mg tablets has been reduced from £49.99 to £39.20 for a 30 tablet pack (the same as the 100 mg dose). This is likely to improve the cost-effectiveness of canagliflozin due to reduced intervention costs. Although the recommendations were optimised, there were not any exclusions based on cost-effectiveness and therefore the lower price of canagliflozin is unlikely to result in the recommendations being extended to cover a broader population.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
There have been no changes to the marketing authorisation since publication of TA315. Also, no changes to the marketing authorisation are proposed that would materially affect the recommendations in the existing guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
The committee could not make recommendations on the dual therapy combination of canagliflozin and a sulfonylurea, because the company did not submit any clinical effectiveness evidence. A small substudy has reported which suggests that canagliflozin is effective as an add-on therapy to a sulfonylurea. Further uncertainties in TA315 related to the lack of long-term follow-up data. This included HbA_{1c} drift over time, as well as adverse events. No longer-term follow-up trials have reported yet, although the 9-year CANVAS study is due to report later in 2017.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
The NICE guideline on type 2 diabetes (NG28) is related. It cross-refers to TA315. Putting TA315 on the static list would have no implications for the guideline. NICE is currently carrying out a standing committee update of NG28, which is looking at the following question: 1. In adults with Type 2 diabetes, what is the clinical effectiveness of SGLT-2 inhibitors on cardiovascular outcomes? However, this is not an update of any of the TAs on SGLT-2 inhibitors but aimed at producing guidance supplementary to them. *See Appendix C for a list of related NICE guidance.*

4. Equalities issues

No equality and diversity issues were raised in the original guidance.

GE paper sign off: Meindert Boysen, 28 July 2017

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Appendix A – Information from existing guidance

5. Original remit

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

6. Current guidance

1.1 Canagliflozin 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 Canagliflozin 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 Canagliflozin 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 canagliflozin 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

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 specify STA or MTA 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 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

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

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

Type 2 diabetes in adults: management (2015 updated 2016) NICE guideline 28.

A partial update is in progress, publication is expected December 2017. One of the questions to be addressed in the update is "In adults with Type 2 diabetes, what is the clinical effectiveness of SGLT-2 inhibitors on cardiovascular outcomes?"

In progress

No relevant information was found.

Referred - QSs and CGs

No relevant information was found.

Suspended/terminated

No relevant information was found.

2. Details of new products

In scoping:

- 1159 - Ertugliflozin with metformin for patients with type 2 diabetes mellitus with inadequate glycaemia control on metformin; add on therapy

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
"2.2 Canagliflozin has a European marketing authorisation for treating type 2 diabetes in adults aged 18 years and older to improve glycaemic control as: • monotherapy 'when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered	The price of the 300 mg tablets has been reduced from £49.99 to £39.20 for a 30 tablet pack (the same as the 100 mg dose), according to eBNF February 2017. The indication remains the same.

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
inappropriate due to intolerance or contraindications' • add-on therapy 'with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control'. "2.4 According to the British national formulary (April 2014), the drug's price (excluding VAT) is £39.20 for canagliflozin 100 mg (30 tablets) and £49.99 for canagliflozin 300 mg (30 tablets). The expected annual cost of canagliflozin is £476.93 for the 100 mg daily dosage and £608.21 for the 300 mg daily dosage. Costs may vary in different settings because of negotiated procurement discounts."	

4. Registered and unpublished trials

Trial name and registration number	Details
A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus CANVAS-R NCT01989754 *Primary outcome: Number of participants with progression of albuminuria.* *Secondary outcomes:* • *Composite Endpoint of Death From Cardiovascular (CV) Causes or Hospitalization for Heart Failure* • *Death from CV Causes* *Other outcome measures:* • *Major adverse cardiovascular (CV) events (including CV death, nonfatal myocardial infarction (MI), and nonfatal stroke.)*	Phase IV, ongoing not recruiting. Enrolment: 5813 Start date: January 2014 Estimated primary completion date: January 2017
A Randomized, Double-blind, Event-driven, Placebo-controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy CREDENCE NCT02065791	Phase III, currently recruiting. Enrolment: 4200 Start date: February 2014 Estimated primary completion date: February 2019
A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus CANVAS NCT01032629	Phase III, ongoing not recruiting. Enrolment: 4323 Start date: December 2009 Estimated primary completion date: February 2017

5. Relevant services covered by NHS England specialised commissioning

"NHS England commissions insulin-resistant diabetes services for adults and children from Highly Specialist Insulin-resistant Diabetes Centres."

6. Additional information

Safety alerts have been issued by the FDA / MHRA / EMA about canagliflozin (as well as alerts about the drug class) since NICE published TA315 in June 2014. These are summarised in date order below:

- 10 September 2015 FDA Drug Safety Communication: FDA revises the label of canagliflozin to include updates on bone fracture risk and new information on decreased bone mineral density.
- 4 December 2015 FDA Drug Safety Communication: SGLT2 Inhibitors - labels to include warnings about too much acid in the blood and serious urinary tract infections. *"…identified 19 cases of life-threatening blood infections (urosepsis) and kidney infections (pyelonephritis) that started as urinary tract infections with the SGLT2 inhibitors reported to FAERS from March 2013 through October 2014. All 19 patients were hospitalized, and a few required admission to an intensive care unit or dialysis in order to treat kidney failure."*
- EMA 25 February 2016: EMA confirms recommendations to minimise ketoacidosis risk with SGLT2 inhibitors for diabetes: *"Healthcare professionals should be aware of possible atypical cases… Following a review of the cases, EMA recommended updating the product information of SGLT2 inhibitors to list diabetic ketoacidosis as a rare adverse reaction (affecting up to 1 in 1,000 patients)…The benefits of these medicines continue to outweigh the risks in the treatment of type 2 diabetes."*
- 18 May 2016 FDA Drug Safety Communication: Canagliflozin - clinical trial results find increased risk of leg and foot amputations. *The MHRA issued a drug safety update on 15 June 2016 saying "A signal of increased lower limb amputation (primarily of the toe) in people taking canagliflozin compared with placebo in a clinical trial in high cardiovascular risk patients is currently under investigation."*
- 14 June 2016 FDA Drug Safety Communication: Canagliflozin - strengthened kidney warnings. *"…we have revised the warnings in the drug labels to include information about acute kidney injury and added recommendations to minimize this risk."*
- EMA 24 February 2017: CHMP opinion SGLT2 inhibitors: information on potential risk of toe amputation to be included in prescribing information.

Appendix D – References

Fulcher, G. et al., (2015) Efficacy and Safety of Canagliflozin Used in Conjunction with Sulfonylurea in Patients with Type 2 Diabetes Mellitus: A Randomized, Controlled Trial. *Diabetes therapy research, and treatment and education of diabetes and related disorders* 6(3), 289-302

Kaur, K. et al., (2015) Efficacy and safety of canagliflozin among patients with type 2 diabetes mellitus: A systematic review and meta-analysis. *Indian journal of endocrinology and metabolism* 19(6), 705-21

Pfeifer, M. et al., 2017) Effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, on blood pressure and markers of arterial stiffness in patients with type 2 diabetes mellitus: a post hoc analysis. *Cardiovascular diabetology* 16(1), 29

Yang, T. et al., (2015) Efficacy and tolerability of canagliflozin as add-on to metformin in the treatment of type 2 diabetes mellitus: A meta-analysis. *European journal of clinical pharmacology* 71(11), 1,325-1,332

Zhong, M. et al., (2016) Therapeutic effect of canagliflozin on type 2 diabetes mellitus: A systematic review and meta-analysis. *International journal of clinical and experimental medicine* 9(5), 7,807-7,817