NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Review Proposal Project (RPP) decision paper

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

Final recommendation post consultation
The guidance should be transferred to the 'static guidance list'.

1. Background

This guidance was issued in June 2014

At the Guidance Executive meeting of 8 August 2017 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

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

3. Rationale for selecting this proposal

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 See Appendix C for further details of ongoing and unpublished studies.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 in combination 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.

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: Boehringer Ingelheim **Response to proposal:** Boehringer Ingelheim believes that important safety evidence from the cardiovascular outcomes trial CANVAS should be part of the consideration of this review. When the guidance TA315 was published in June 2014, it was clearly expressed by the Appraisal Committee that longer-term data are needed for the adverse events for canagliflozin (Section 4.13 of guidance TA315; and summary of Appraisal Committee's key conclusions) "…The Committee concluded that the short-term adverse events for canagliflozin (100 mg and 300 mg doses) were manageable and that further data for longer-term outcomes are still needed, particularly for cardiovascular adverse events." Since the original appraisal in 2014, long-term adverse events data for canagliflozin from the CANVAS Programme have become available. 2 The study concluded that for patients with type 2 diabetes and an elevated risk of cardiovascular (CV) disease, canagliflozin had a lower risk of CV events but a greater risk of amputation, primarily at the level of the toe or metatarsal, than those who received placebo. The safety concern regarding amputation is considered significant and is now reflected in section 4.4 of the summary of product characteristics (SPC) for canagliflozin. 3 In the CANVAS trial, it was also found that the rate of all fracture was higher with canagliflozin than with placebo. 2 We believe these data significantly affect not only the risk:benefit profile of canagliflozin but also consequently its cost-effectiveness. We therefore suggest that the clinical and economic implication of the CANVAS study should be fully considered before putting TA315 into the static list. In addition to the safety concerns relating to canagliflozin, both CANVAS and EMPA-REG OUTCOME (empagliflozin) trials have reported beneficial CV outcomes. 2,4 As such, we	**Comment from Technology Appraisals** Thank you for your comments. The impact of microvascular complications on quality of life and costs was included in the economic model. These were not key model drivers and it is unlikely that increasing the rate of amputation would have a significant impact on the cost effectiveness of canagliflozin. It is also noted that while the EMA has updated the summary of product characteristics for canagliflozin to reflect these safety concerns, its Pharmacovigilance Risk Assessment Committee concluded that the benefits of canagliflozin continue to outweigh the risks. 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

request NICE to consider the CV evidence from these studies in their respective technology appraisal guidance (TA315, TA336 and ID1037).	cotransporter-2 inhibitors on cardiovascular outcomes. No changes to the recommendation are needed.

Respondent: Janssen **Response to proposal:** Agree Janssen agrees with the NICE proposal of transferring the review of TA315 to the 'static guidance list'. Janssen would like to highlight that in the second paragraph of the rationale section, NICE states: "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" We believe that what NICE intends to say is the following, 'effectiveness of canagliflozin in combination with a sulfonylurea'. Just to reinforce that as part of the evidence submitted in TA315, the phase 3 study DIA3009 compared canagliflozin with glimepiride (a sulfonylurea) as part of a dual therapy combination with metformin.	**Comment from Technology Appraisals** Thank you for your comment. The rationale in the decision paper has been updated to reflect this. No changes to the recommendation are needed.

Respondent: Merck Sharp & Dohme UK Ltd **Response to proposal:** No comment	**Comment from Technology Appraisals** No changes to the recommendation are needed.

Respondent: Department of Health **Response to proposal:** No comment	**Comment from Technology Appraisals** No changes to the recommendation are needed.

Paper signed off by: Jenniffer Prescott, 13 October 2017

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