M E M O R A N D U M

From:	Dir/NCD	**To:**	Dir/EML	**Date: 20 May 2021**
Our ref:		**Attention:**		
Your ref:	HQ-2021-DOCS-eMemo-73234	**Through:**		
Originator:		**Subject:**	23rd EXPERT COMMITTEE ON SELECTION AND USE OF ESSENTIAL MEDICINES - COMMENTS ON NCD-RELATED APPLICATIONS: Endocrine-disorders (diabetes)	

With reference to the 23rd Expert Committee Meeting on Selection and Use of Essential Medicines scheduled to take place from 21 June to 2 July 2021, please find enclosed the NCD Department comments on Endocrine disorders-related applications as requested with the Memorandum HQ-2021-DOCS-eMemo-73234, here attached for ease of reference.

Comments on Cancer-related applications (HQ-2021-DOCS-eMemo-74597) will be sent by Monday, 24 May by separate memorandum.

We remain available should more information be required.

Thank you,

Dr Bente Mikkelsen

ENCLs: (3)

COMMENT ON THE APPLICATION FOR THE INCLUSION OF SODIUM-GLUCOSE COTRANSPORTER-2 (SGLT-2) INHIBITORS IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES 2021, AS ADD-ON TREATMENT FOR TYPE 2 DIABETES

The technical unit supports the application to add SGLT-2 inhibitors to the 21st WHO Model List of Essential Medicines (EML). The focus of the application is the addition of SGLT-2 inhibitors as add on treatment for non-pregnant adults with T2D with or at high risk of CVD and/or diabetic nephropathy. The reasons for the support are:

- It is a useful and effective drug and lowers mortality and some morbidities
- Acceptable adverse effects risk profile compared with other glucose-lowering drugs and placebo.

Cost -analysis of SGLT2-inhibitors in LMICs are lacking. Direct costs are increased, but they might be cost-effective due to improvement in other costly outcomes.

The application is based on a comprehensive review of relevant literature with reference to most updated and comprehensive systematic reviews.

Target population of the application includes non-pregnant adults with T2D and:

- Established CVD.

- Established renal disease.

- High risk of heart disease (according to HEARTS technical package).

Effectiveness

- SGLT-2 inhibitors lower odds of all-cause mortality compared to placebo, DPP-4 inhibitor, sulfonylurea or GLP-1 Receptor agonists (RA) as add-on therapy. The effect on all-cause mortality was most clinically significant in people with established cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease (The Australian Guideline Review). Findings confirmed in Palmer et al.
- protective effect on cardiovascular disease (probably lowered odds of four major CVD events (composite of CV death, non-fatal myocardial infarction, non-fatal stroke plus hospitalization for unstable angina). No difference identified for three major CVD events (composite of CV death, non-fatal myocardial infarction and non-fatal stroke)- The Australian Guideline Review). In Palmer et al reduction in non-fatal myocardial infarction was identified. No difference was identified for stroke.
- Protective effect on renal disease. The effect on kidney failure were most clinically significant in people with established cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease (The Australian Guideline Review). Findings confirmed in Palmer et al.
- There is little or no evidence for an effect of SGLT-2 inhibitors on limb amputation, blindness, eye disease, neuropathic pain, or health related quality of life (Palmer et al).
- SGLT-2 inhibitors reduce admission to hospital for heart failure (Australian Guideline Review and Palmer et al).

Adverse effects

- -SGLT-2 inhibitors incur lower odds of serious adverse events (SAEs) than standard care (The Australian Guideline Review).
- No increased risk of severe hypoglycaemia (The Australian Guideline Review, Palmer et al). In Schorling et al Empagliflozin was not associated with a higher rate of confirmed hypoglycaemia versus placebo, except in patients co-administered insulin and/or a sulfonylurea.
- The increased risk of genital mycotic infections with SGLT-2 inhibitor treatment in both men and women has been consistent across all clinical trials. This can often be managed with topical antifungal medication and self-care.
- Fournier's gangrene is uncommon (55 post-marketing cases identified by FDA in 6 years of SGLT-2 inhibitor use)
- There are conflicting data about SGLT-2 inhibitors and increased risk of urinary tract infections.
- The frequency of AEs consistent with volume depletion was similar across groups, but higher with empagliflozin in patients aged 75 to 85 years and those on loop diuretics at baseline (Schorling et al). The risk of symptoms of volume depletion is overall small (McGill et al).
- Diabetic ketoacidosis is increased in people treated with SGLT-2 inhibitors compared with placebo or other glucose-lowering drugs. Peto Odds Ratio 2.13, 95% CI 1.38 to 3.27). However, Palmer et al and Schorling et al did not find any increased risk of ketoacidosis compared with placebo.
- There has been suspicion of increased risk of bone fracture – this finding has not been confirmed in recent systematic reviews.
- There has been suspicion of increased risk of amputation with SGLT-2 treatment. Based on existing data, there is no consistent evidence of SGLT-2 inhibitor exposure increases the risk of amputation.

Affordability

- The data regarding the costs in the application is not convincing. The systematic reviews in this section only contain data from HICs or limited data from LMICs. Besides large heterogeneity, indication of publication bias for the comparison SGLT-2 inhibitors vs. SUs was identified (Bagepally et al).
- Table 4 shows consistently higher costs of all subtypes of SGLT-2 inhibitors compared with SU, but lower costs compared with GLP-1 RA.

Conclusion

People with type 2 diabetes (T2D) have about a twofold increased risk for cardiovascular disease (CVD), and CVD is the main cause of death in people with T2D. Management of blood glucose, in addition to treatment of other CVD risk factors, is a central part of diabetes management. Therefore, glucose-lowering interventions, that besides lowering blood glucose also lower the risk of cardiovascular disease will be an asset as a treatment option for people with T2D.

This application provides an up-to-date evidence overview of most recent literature on SGLT-2 inhibitors, and have included evidence from systematic reviews, where possible.

Two major systematic reviews in this application (The Australian Guideline Review and Palmer et al) included people with varied baseline risk of cardiovascular disease, but the major proportion of the

included trials had cardiovascular disease and/or chronic kidney disease as eligibility criteria. Therefore, most of the evidence is based on participants people with T2D with high risk of CVD. The main comparison for the meta-analysis is SGLT-2 inhibitors compared with placebo added to standard treatment. The overall quality of the evidence is good, with data from several large randomised clinical trials combined into meta-analyses. The confidence in the effect estimates on all-cause mortality, CVD, kidney failure and heart failure is moderate for people with lowest risk of CVD. There is high certainty of the effect estimates on all-cause mortality, CVD, kidney failure and heart failure in the remaining (higher) risk groups. It is the groups with higher risk of CVD, which this application suggests as target population for the addition of SGLT-2 inhibitors. There are increased risks of certain adverse events (e.g., genital infections). The data on risk of ketoacidosis are not consistent, but risk might be increased. The risk of serious adverse events seems to be low. We judge that the benefits of SGLT-2 inhibitors outweigh the harms. The glucose-lowering effect of the SGLT-2 inhibitors is modest, and is not the main reason for recommending SGLT-2 inhibitors be included in the EML.

Currently, the add-on to metformin therapy in people with diabetes could be sulphonylureas or human insulin. With the addition of SGLT-2 inhibitors some people will be initiated on SGLT-2 inhibitors instead of sulphonylureas or insulin. Very few trials have compared sulphonylurea with a SGLT-2 inhibitor, so the superiority of SGLT-2 inhibitors should therefore be interpreted with caution. The basis for the recommendation is therefore based on the comparison of SGLT-2 inhibitors compared with placebo in addition to standard treatment (which could have included any combination of hypoglycaemic agents).

The direct costs of SGLT-2 inhibitors are higher than for sulphonylureas, but they might be cost-effective due to reduction in costly clinical events, including death. Data from LMICs are sparse.

With the arguments of convincing effect on clinically important outcomes, including reduction in mortality, we recommend the addition of the SGLT-2 inhibitors to the updated EML. The increased costs and risk profile probably does not outweigh the benefit of the SGLT-2 inhibitors.

COMMENT ON THE APPLICATION TO ADD (ULTRA) LONG-ACTING INSULIN ANALOGUES TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES

The technical unit does not support the application to add long-acting insulin analogues nor their biosimilars to the 23rd WHO Model List of Essential Medicines (EML). The application was not developed in consultation with this WHO department.
The application proposes the addition of long-acting and ultra-long-acting insulin analogues to the WHO List of Essential Medicines for type 1 and type 2 diabetes mellitus for adults and children (aged 2 years and above).

The insulin analogues applied for are:

- glargine 100 U/mL
- detemir 100U/mL
- degludec 100 U/mL

The applicants have performed a search for systematic reviews, but have not interpreted data from the systematic reviews critically.

The applicants claim that new evidence has become available since the 2019 review which was basis for the 2019 application. In the 2019 application, the target population was people with type 1 diabetes. For type 1 diabetes no new studies comparing insulin analogues with human insulin have been completed since the last application. However, additional, hitherto unpublished data, are included in the 2021 Cochrane review. These additional data do not support the use of insulin analogues on account of their superiority to human insulin. The current application also includes people with type 2 diabetes as the target population. No major studies comparing insulin analogues with human insulin have been published since 2019. The Cochrane review including people with type 2 diabetes has included 1 study published since the last application for adding insulin analogues to the EML; this study was published in 2019 and includes 63 people with type 2 diabetes and CKD stage 3 and 4. These data do not change the overall estimate of the hypoglycaemia evaluation of insulin glargine vs. NPH (no difference for hypoglycaemia was identified). There is therefore no solid evidence base to change the judgement of 2019.

The applicants mention the use of long-acting insulin analogues is expanding in many countries, however, this could very likely be due to the fact that the market is largely dominated by three large pharmaceutical companies, which all have interest in promoting insulin analogues.

The authors state that there are lower rates of insulin-induced hypoglycaemic events when using long-acting analogues instead of insulin NPH. This is not supported by the evidence. Please see further elaboration below.

Several systematic reviews comparing the benefits and harms of insulin analogues with NPH insulin exist, but several of the ones cited in this application have methodological deficiencies due to lack of identification of all relevant studies, missing analysis of clinical study reports (CSR) and poor 'Risk of bias' assessment (e.g., Laranjeira 2018, Tricco 2021).

The Laranjeira 2018 had already been published when the EML was revised in 2019 and does not provide updated evidence.

Tricco et al only included people with type 1 diabetes above 16 years. The review does also not include any trials comparing insulin analogues with human insulin published since 2018 (i.e. since the last EML application). Besides, the quality of this review gives rise to concerns due to severe methodological shortcomings. Some of them are listed below :

- Tricco et al has included 65 unique studies, but on reading the review it becomes apparent that less than half of the included studies compared insulin analogues (detemir, glargine) with NPH insulin. No trials compared NPH with degludec. Most of the included trials included were comparisons of one insulin analogue with another insulin analogue or the identical or biosimilar insulin analogue with different treatment schemes.

- Another very important pitfall to take into consideration when reading the review by Tricco et al. is that they have not identified co-publications of same trials correctly – so several trials are counted more than once (eg, the populations in De Leeuw 2005 and Vague 2003 are the same populations; ditto for Witthaus 2001 and Home 2005).

- Compared with the Cochrane review on the same topic, it appears that some unpublished data are lacking in the Tricco et al review.

- The difference in glycaemic control identified in Tricco et al. is lower than values usually considered to be clinically relevant.

The findings in the review of Almeida et al 2018 are misleadingly presented. The applicants report that 5 studies reported statistically significant differences in quality of life in certain quality of life domains, but fail to report the overall conclusion of the Almeida 2018 review – namely that there was no consistent difference in QoL or patient-reported outcomes when the findings from the eight included studies were

collated. The Almeida 2018 review includes both data from cohort and RCTs in people with type 1 diabetes. More updated data are available (Hemmingsen et al 2021) evaluating quality of life comparing insulin analogues with human insulin from RCTs.

The systematic review by Cherubini et al. 2019 did not find any advantages of any type of long-acting insulin compared to NPH.

The review by Hemmingsen et al has fewer trials than Tricco et al – partly because its authors succeeded in correctly identifying co-publications of the same study population. The sample size was therefore smaller, but exclusively based on direct evidence. The reduction in severe hypoglycaemia for detemir vs. NPH was only moderate. The 95% prediction interval indicated inconsistency which means that if we performed an additional study comparing insulin detemir with NPH insulin there may not be a clear difference in the risk of severe hypoglycaemia for this comparison.

The review by Semlitsch et al includes people with T2D and showed a modest reduction in severe hypoglycaemia with detemir compared with NPH. However, serious hypoglycaemic events were rare. Approximately one in 100 people treated with insulin detemir instead of NPH insulin benefited. Besides, the results might only be applicable to people targeting lower glycaemic threshold than recommended in existing guidelines, as low glycaemic target was applied in trials. The confidence in the evidence for this outcome was graded as low.

The review from Czech et al 2015 includes people with T1D and T2D is based on observational studies and a modelling to estimate events – the finding of this review is of very low certainty.

The review by Singh 2015 included 2 RCTs (n = 114) and one cohort (n = 172) comparing long-acting insulin analog vs. NPH insulin in hospitalized adults. The result of this review is doubtful. In the RCTs the review authors did not find any difference in the risk of severe hypoglycaemic.

The review by Sv et al does not favour any long-acting insulin.

The section on costs of insulin, the largest study (ACCISS) performed in LMICs does not support the assertion that insulin analogues are cost effective.

Some cost-effectiveness analyses presented in the application report cost-effectiveness compared to human insulins even though the procurement costs are higher. This is due to assumed/modelled health benefits such as lower rates of hypoglycaemia. However, the rate of severe hypoglycaemia was only reduced for insulin Levemir (detemir) and this to a doubtful and at best modest extent in the Cochrane reviews.

There is a lack of randomised controlled trials investigating the effect of long-acting insulin analogues compared with human insulin in humanitarian settings and in fasting during Ramadan. In humanitarian settings the main problem is access to the needed insulin, and the focus should be on having insulin accessible. There is no good quality evidence to support preference for insulin analogues in circumstances of irregular or insecure food supplies. Clinical data are still needed to establish the clinical impact of pharmacodynamic differences between NPH and insulin analogues in humanitarian settings and during Ramadan.