Response from Bernd Richter and Bianca Hemmingsen to ...

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Innovation, Access and Use (IAU)
Department of Essential Medicines and Health Products
20 Avenue Appia
CH-1211 Geneva 27
Email: emlsecretariat@who.int

ESSENTIAL MEDICINES LIST (EML) 2019

Application for the inclusion of long acting insulin analogues including biosimilar in the WHO Model List of Essential Medicines, as treatments used for patients with diabetes type 1

by Andrea C. Tricco, Huda M. Ashoor, Jesmin Antony, Zachary Bouck, Myanca Rodrigues, Ba’ Pham, Paul A. Khan, Vera Nincic, Nazia Darvesh, Fatemeh Yazdi, Marco Ghassemi, John D. Ivory, Wanrudee Isaranuwatchai, Areti Angeliki Veroniki, Catherine H. Yu, and Sharon E. Straus

We wish to record our objection to the proposed inclusion of long-acting insulin analogues including biosimilars for type 1 diabetes mellitus in the WHO’s Model EML 2019. Based on the results of their systematic review (SR) and network meta-analysis (NMA) the applicants propose “that Expert Committee on the Selection and Use of Essential Medicines considers the addition of long acting insulin analogues (detemir insulin, glargine insulin (follow-on product or biosimilar (a)basaglar, MK-1293), degludec insulin) to the core list of anti-diabetes medicines for patients with type 1 diabetes” (1). The applicants published a previous systematic review and NMA analysing long-acting insulin analogues versus intermediate-acting insulins in people with type 1 diabetes mellitus but did not include biosimilar insulins (2).

In our opinion the applicants have not provided a convincing case for the inclusion of long-acting insulin analogues in the WHO Model List of Essential Medicines 2019, as treatments used for patients with type 1 diabetes mellitus. We base our objections on the arguments as specified below:

The objectives to investigate the comparative efficacy and safety of intermediate, (ultra)long-acting and
biosimilar (follow-on) insulin appear unclear. Applicants stated “Our aim was to systematically review and evaluate the comparative effectiveness and safety of intermediate-/long-acting insulin products and intermediate-/long-acting/ultra-long-acting biosimilar insulin products in patients with type 1 diabetes mellitus (T1DM)” and “We also aimed to determine whether intermediate/long-acting/ultra-long-acting biosimilar insulin products should be listed as a replacements for reference intermediate- and long-acting insulin products (including insulin analogues) when the latter products are not available (due to cost or supply issues)”. A thorough reading of the SR and NMA discloses that applicants compared all basal insulins with each other. The current 20th List (March 2017, amended August 2017) ‘WHO Model List of Essential Medicines’ mentions in section 18.5 (“Insulins and other medicines used for diabetes”) gliclazide, glucagon, insulin injection (soluble), intermediate-acting insulin and metformin (3). Therefore, our critique focuses on the single relevant comparison of (ultra)long-acting insulin analogues to (mainly) NPH insulin.

Of the 63 analysed randomised controlled trials (RCTs) including 1 non-RCT (see appendix table 1 in (1)) only 26 RCTs (41%) compared insulin analogues (detemir, glargine) with NPH insulin. There were no RCTs comparing degludec with NPH insulin. Two RCTs compared an irrelevant NPH insulin regimen (four times daily) with glargine and 8 RCTs compared NPH/Lente with each other. There were 27 RCTs (43%) comparing one insulin analogue versus another insulin analogue or the identical or biosimilar insulin analogue with different insulin treatment schemes. A total of 32% of RCTs had a crossover design and 22% investigated non-inferiority.

Body of the evidence

It is unclear whether trials registers were searched (especially ClinicalTrials.gov and WHO ICTRP portal). When checking stated NCT identifiers in the publications listed by the applicants ClinicalTrials.gov provided a wealth of additional and more elaborate information, not only by means of published study results in this database but also through links to detailed Clinical Study Reports (at least on 16 RCTs) and Clinical Study Synopses (at least on 4 RCTs). This additional information consisting of thousands of pages on approx. one third of the total body of RCTs evidence was obviously not evaluated (4). Moreover, the US Food and Drug Administration (FDA) has very comprehensive medical and statistical reviews of insulin analogues which should have been evaluated as well - these reports could contain information on additional outcomes of already included studies as well as new unidentified clinical trials. If a SR, like the one the applicants submitted, is solely based on published data, there is a high risk of over-estimating intervention effects (5).
Methods

The statistical analysis method for NMA analysis was not detailed. For all analyses contrasting basal insulin class (i.e. intermediate-acting insulin vs long-acting insulin analogues vs ultra-long acting insulin analogue) there were no closed loops in the NMA diagram resulting in indirect comparisons of treatments only (Appendix Figure 3 in (1)). According to the *Cochrane Handbook for Systematic Reviews of Interventions* indirect comparisons provide observational evidence and may suffer the biases of observational studies, such as confounding. The validity of an indirect comparison relies on the assumption that the different sets of RCTs are similar, on average, in all important factors other than the intervention comparison being made (6). Transitivity is the core assumption underlying the validity of indirect comparisons. We think that clinical and methodological differences of the included RCTs were sufficiently large to cause intransitivity. It is especially unclear how authors handled analysis of the transitivity assumption especially for study design (crossover RCTs) and length of follow-up providing information on HbA1c and all-cause hypoglycaemia only (Appendix Table 9 in (1)). The large number of crossover RCTs imposes difficulties for NMA and it is unclear how applicants handled this problem (7).

A majority of RCTs had an unclear risk of selection bias which obviously was not clarified through study author contact (review authors claim that they contacted trial authors of 89 studies with feedback on 18 studies). Nineteen per cent of RCTs had a high risk of attrition bias, 6% a high risk of selective reporting (probably more had authors contrasted publications to Clinical Study Reports) and 71% a high risk of other risk of bias (e.g. funding bias). Authors stated that they deemed all outcomes of interest as “objective” and assigned a low risk of performance and detection bias. This approach was not adequate because amongst their outcomes especially quality of life, weight change, hypoglycaemia and adverse events were not “objective”.

The applicants did not employ the GRADE system to describe the overall certainty of the evidence rating the certainty of estimates of treatment effects according to study limitations such as risk of bias, inconsistency, indirectness, imprecision and publication bias. The *Cochrane Handbook for Systematic Reviews of Interventions* recommends that for NMA “the confidence in the evidence should be assessed for each intervention effects that is reported in the results” (6). There are several publications on how to achieve this request (8-10).
Results

With regard to NMA results according to basal insulin class (intermediate-acting, long-acting, ultra long-acting) it is apparent from Appendix table 6 and Appendix figure 2 (1) that almost all analyses (HbA1c, vascular complications, weight change, all-cause hypoglycaemic episodes and nocturnal hypoglycaemic episodes, total adverse events, serious adverse events, dropouts due to adverse events) showed 95% predictive intervals ranging from beneficial to harmful effects and thus included the null effect. The predictive interval specifies a predicted range for the true treatment effect of a future study. For serious hypoglycaemic episodes only the comparison of long-acting o.d. insulin versus intermediate-acting o.d. insulin resulted in a statistically significant reduction in favour of long-acting insulin analogue as indicated by the predictive interval (no longer the case if adjusted for short bolus insulin covariate). The four RCTs contributing to this result would need to be especially evaluated for risk of bias to establish an adequate evaluation of the transitivity assumption (see Appendix table 9 in (1)) because definition of hypoglycaemia is bias-prone (only 3 of 33 included studies reporting serious hypoglycaemia associated this event with hard clinical data such as help from medical persons, medical assistance or the use of glucagon injection, coma or car accident). The way severe/serious hypoglycaemia is defined is bias-prone. For example, hypoglycaemia leading to coma or fulfilling criteria for established definitions of serious adverse events is less susceptible to risk of bias than ‘patients unable to treat themselves’ or ‘help from third party’. In addition, applicants did not provide information about whether in some included studies patients had participated in a patient education and management programme, which is known to significantly affect both metabolic control and hypoglycaemia (11).

In conclusion we think that the present application does not provide convincing evidence to add (ultra)long-acting insulin analogues to the ESSENTIAL MEDICINES LIST (EML).

Prof. Bernd Richter, MD,PhD Coordinating Editor & Bianca Hemmingsen, MD Deputy Coordinating Editor
Cochrane Metabolic and Endocrine Disorders Review Group
Institute of General Practice
Medical Faculty of the Heinrich-Heine University Duesseldorf
PO Box 101007, 40001 Duesseldorf, Germany
Office address: Werdener Str. 4, 40227 Duesseldorf, Germany
Phone +49 211 811 8773 | Fax +49 211 81 015 18773
richterb@uni-duesseldorf.de; biancahemmingsen@hotmail.com
www.endoc.cochrane.org
References


(4) ClinicalTrials.gov (last accessed 28 February 2019) - Studies with links to manufacturer’s Clinical Study Reports/Synopses:
NCT00095082; NCT00117780; NCT00184665; NCT00312104; NCT00474045; NCT00595374; NCT00612040; NCT00841087; NCT00961324; NCT00982228; NCT01002768; NCT01068665; NCT01074268; NCT01076634; NCT01079234; NCT01135927; NCT01697657; NCT01704417; NCT02034513; NCT02536859

(5) Jefferson T, Doshi P, Boutron I, Golder S, Heneghan C, Hodkinson Aet al. When to include clinical study reports and regulatory documents in systematic reviews. BMJ Evid Based Med 2018;23(6):210-217


(10) A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ 2015;350:h3326