UNIVERSITÉ
DE GENÈVE
FACULTÉ DE MÉDECINE

Department of Health and Community Medicine
Division of Tropical and Humanitarian Medicine
Rue Gabrielle-Perret-Gentil 6
CH-1211 Genève 14, Suisse
Tél: +41 (0)22 372 9503
Fax: +41 (0)22 372 9505
E-mail: David.Beran@unige.ch

The Secretary
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
20 Avenue Appia
1211 Geneva 27

20 May 2021

Dear Members of the Expert Committee,

Re: Application to add (ultra-)long-acting insulin analogues to the WHO Model List of Essential Medicines

I hereby submit this letter against the inclusion of (ultra-)long-acting insulin analogues on the World Health Organization's (WHO) Model Essential Medicines List (EML) for the consideration by the Expert Committee.

The current submission to the WHO Expert Committee for inclusion of long-acting analogues to the WHO's Model EML is the fourth after proposals in 2011, 2017 and 2019. Previous overall comments from the Expert Committees' have been:

- 2011 – *"insulin analogues currently offer no clinical advantage over recombinant human insulin…"*
- 2017 – recommended to not include analogue insulin on the EML and EML for children due to *"small magnitude of benefit and current high price compared to human insulin."*
- 2019 – Did not recommend the addition of insulin analogues to the EML, reiterating the conclusion of the 2017 Expert Committee … *"the available evidence shows efficacy and safety advantages of analogues compared to human insulin which are insufficiently large to justify the cost differential that continues to exist."*

The current submission fails to address previous concerns related to the high prices of analogue insulin compared to human insulin as well as provide and build upon previous reviews of the evidence in a convincing way. Any submission for the inclusion of analogues on the WHO Model EML needs to address these two fundamental issues, by: firstly presenting new evidence highlighting the effectiveness of analogues versus human insulin; and secondly

showing that the price differential between analogue and human insulin is smaller or no longer present.

With regards to the evidence, the application states that *"Recent systematic reviews, including Cochrane Reviews and the Lancet Commission on Diabetes, have endorsed their use"* in referring to analogue insulin. This is incorrect. Firstly, the Lancet Commission on Diabetes [1] was not a systematic review of the evidence on the use of analogue insulin. The authors also refer to a Network Meta-Analysis by Tricco et al. [2] as well as two Cochrane Reviews by Semlitsch et al. [3] and Hemmingsen et al. [4]

In looking at the Tricco et al. [2] study that the authors use to argue for the inclusion of analogue insulins for children and adults as well as for type 1 and type 2 diabetes, this study only included subjects above the age of 16 and was only for type 1 diabetes.

Secondly, for the two Cochrane Reviews, the authors of this application incorrectly quote the results, as these Reviews do not provide any "endorsement" of the use of analogue insulin. The authors fail to include that Semlitsch et al. [3] in their conclusions state "*Approximately one in 100 people treated with insulin detemir instead of NPH insulin benefited. In the studies, low blood glucose and HbA1c targets, corresponding to near normal or even non-diabetic blood glucose levels, were set. Therefore, results from the studies are only applicable to people in whom such low blood glucose concentrations are targeted. However, current guidelines recommend less-intensive blood glucose lowering for most people with type 2 diabetes in daily practice (e.g. people with cardiovascular diseases, a long history of type 2 diabetes, who are susceptible to hypoglycaemia or older people). Additionally, low-certainty evidence and trial designs that did not conform with current clinical practice meant it remains unclear if the same effects will be observed in daily clinical practice. Most trials did not report patient-relevant outcomes."* Based on this, the authors can hardly be "endorsing" the use of analogues in the management of type 2 diabetes. In addition the recent Cochrane Review entitled, "(Ultra-) long-acting insulin analogues for people with type 1 diabetes mellitus" by Hemmingsen et al. 2021 [4] states: *"Both insulin detemir and insulin glargine compared with NPH insulin did not show benefits or harms for severe nocturnal hypoglycaemia. For all other main outcomes with overall low risk of bias and comparing insulin analogues with each other, there was no true beneficial or harmful effect for any intervention."* Therefore the authors fail to provide any new evidence that would justify the inclusion of analogues on the WHO Essential Medicines List.

The authors state that prices of analogues are decreasing, but the data presented on pricing in no way shows that the price of analogue insulin has changed since the previous submissions. With regards to decreasing prices the arguments made by the authors are all hypothetical at this stage. Although I agree that biosimilar manufacturers offer an opportunity to lower prices of analogue insulin, this is yet to be seen in practice and any changes in prices to date have not significantly decreased the gap between the prices of analogue and human insulin.

The data referenced from the Addressing the Challenges and Constraints of Insulin Sources and Supply (ACCISS) Study (which I am involved with) show significant differences in the prices between analogue and human insulin. The report prepared by Godman [5], which in my view has many limitations is used as another reference to show that prices of analogue insulin have decreased. Firstly, the focus on Europe by Godman is a serious limitation and the applicability of such findings to low- and middle-income countries merits further consideration. Also the other non-European countries where the data was collected as well as the Methods warrant discussion. Godman rightly highlights the lack of access to insulin in many African settings, but fails to state that including analogue insulin will do little to change this. The prices highlighted in table 1 clearly show a significant price differential with vials of analogue insulin being 3.3 and 3.9 times higher. Overall price comparisons are difficult in the material provided as these are not standardized to for example a vial equivalent. The section on discussing access to insulin in Africa would tend to highlight a high price differential as well as serious issues of access to insulin which by adding analogue insulin to the WHO Model EML might compound these issues versus solving them. For Bangladesh no prices are given for human insulin, but clearly analogue insulin cannot be affordable at the prices quoted in table 2. Again the section on India, South Korea, Malaysia and Pakistan add nothing to justify the inclusion of analogue insulin on the WHO Model EML as there are no price comparisons presented, but just the changes in the insulin market and the prices of analogues as well as uptake of biosimilars. In the section on Latin America and Canada, again if the argument is that the cost of analogues has decreased the data presented fail to convincingly show this as it would seem that the financial burden has increased due to higher use of analogues. Data for Europe which focuses on biosimilar uptake shows that these are quite low which is contrary to what is stated in the application about increases in biosimilars impacting the overall market.

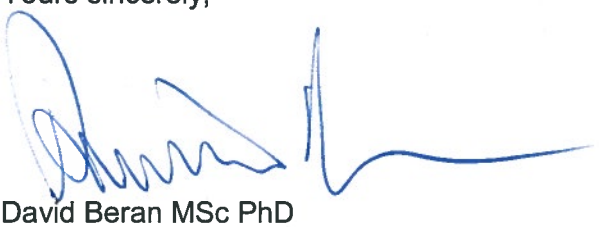
Beyond the evidence and price, as well as issues raised in this submission about biosimilars and their potential impact on the global market, access to insulin needs to be positioned within a wider historical and market context. Although we are celebrating the centenary of insulin's discovery as a treatment for diabetes, access in many contexts, as alluded to in the submission, remains poor. The current submission negates that the insulin market is controlled by three large multi-national corporations and the impact this can have on the overall market and access for individuals. This concentration of the market needs to be considered in any health-related approach, especially including analogue insulin on the WHO's Model EML. This decision might precipitate the disappearance of human insulin resulting in less choice and access as well as higher prices for individuals and health systems. Although it has been argued that price should not be a precondition for inclusion of a medicine on the WHO Model EML, human insulin remains an effective and more affordable option.

The authors of the application state that the *"EML should be forward-looking and accept reasonable expectation that a product's price will significantly reduce in the near-to-medium-term (e.g. 5 years), particularly if policy approaches that favour biosimilars and cost-containment are pursued at a country level."* However, they fail to mention the Global Diabetes Compact or the recommendations from the 2019 Expert Committee on actions WHO should be taking to improve access to insulin. It would seem that these initiatives should be allowed to advance to create the propitious policies and global context before the addition of analogue insulin to the WHO Model EML.

As per my submission against the inclusion of analogue insulin to the Expert Committee in 2019, in my view the most important question should be whether or not adding analogue insulin to the WHO Model EML will impact access to insulin and outcomes for people with diabetes. The answer is unfortunately no, given that human insulin still fails to reach those in need, due to various global and national factors. With the launch of the Global Diabetes Compact in April 2021 the WHO is finally addressing some of the action points included in the recommendations from the 2019 Expert Committee which will hopefully tackle the different factors needed to guarantee access to insulin for all those in need. Until this is done adding analogue insulin may create more problems than it solves.

In advance I would like to thank the Expert Committee for taking the time to consider my arguments, and remain,

Yours sincerely,



David Beran MSc PhD

Assistant Professor

University of Geneva

Faculty of Medicine

Division of Tropical and Humanitarian Medicine

and Faculty Diabetes Centre

References

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[2] Tricco AC, Ashoor HM, Antony J, et al. (2021) Comparative Efficacy and Safety of Ultra-Long-Acting, Long-Acting, Intermediate-Acting, and Biosimilar Insulins for Type 1 Diabetes Mellitus: a Systematic Review and Network Meta-Analysis. J Gen Intern Med. 10.1007/s11606-021-06642-7

[3] Semlitsch T, Engler J, Siebenhofer A, Jeitler K, Berghold A, Horvath K (2020) (Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev 11: CD005613. 10.1002/14651858.CD005613.pub4

[4] Hemmingsen B, Metzendorf MI, Richter B (2021) (Ultra-)long-acting insulin analogues for people with type 1 diabetes mellitus. Cochrane Database Syst Rev 3: CD013498. 10.1002/14651858.CD013498.pub2

[5] Godman B (2021) Report for the 2021 WHO Expert Committee on Selection and Use of Essential Medicines on recent insulin price trends in a sample of countries (including but not necessarily limited to low- and middle-income countries), exploring key issues and suggestions for the future to enhance utilisation and funding for long-acting insulin analogues given current concerns.