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April 15, 2025

Re: **A.18 Insulin, analogue rapid-acting – diabetes mellitus**

Dear WHO Essential Medicines List team,

I am strongly in favour of the application submitted by T1International to add analogue rapid-acting insulins for treatment of diabetes mellitus to the WHO Essential Medicines List (EML).

I am writing this statement in my personal capacity. I am a global health consultant who has worked with the WHO, as well as MSF and other global health organizations. I have been involved with diabetes research projects in the Sultanate of Oman, Lebanon and Canada, as well as global initiatives including the WHO Global Diabetes Compact. I am also a past trustee of T1International UK and USA, and a current trustee of the Global Alliance for Chronic Diseases. I also have been living with type 1 diabetes for 25+ years. In that time, I have personally taken for treatment: insulin regular human, NPH insulin, insulin glargine, insulin detemir and now take a basal/bolus regime of insulin lispro and insulin degludec.

The reasons for my support of this application are as follows.

First is the marked reduction of hypoglycaemic events seen in populations with diabetes taking rapid-acting insulin analogues relative to human insulin. Hypoglycaemic events are life-threatening, highly disruptive and impede the ability of people living with diabetes to work and perform everyday tasks. The ability to measure blood glucose levels is greatly reduced in low- and middle-income country households relative to high income country households, further strengthening the need to reduce the frequency and severity of hypoglycaemic reactions. Reduction of hypoglycaemic reactions is a major reason to support inclusion of analogue rapid-acting insulins – not a fringe benefit.

Studies supporting the reduction in hyperglycaemia are below:

Melo KFS, Bahia LR, Pasinato B, Porfirio GJM, Martimbianco AL, Riera R, Calliari LEP, Minicucci WJ, Turatti LAA, Pedrosa HC, Schaan BD. Short-acting insulin analogues versus regular human insulin on postprandial glucose and hypoglycemia in type 1 diabetes mellitus: a systematic review and meta-analysis. Diabetol Metab Syndr. 2019 Jan 3;11:2. doi: 10.1186/s13098-018-0397-3. PMID: 30622653; PMCID: PMC6317184.

Which concluded: *Short-acting insulin analogues are superior to regular human insulin in T1DM patients for the following outcomes: total hypoglycemic episodes, nocturnal hypoglycemia, severe hypoglycemia, postprandial glucose, and HbA1c.*

Pedersen-Bjergaard U, Kristensen PL, Beck-Nielsen H, Nørgaard K, Perrild H, Christiansen JS, Jensen T, Hougaard P, Parving HH, Thorsteinsson B, Tarnow L. Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): a prospective, randomised, open-label, blinded-endpoint crossover trial. Lancet Diabetes Endocrinol. 2014 Jul;2(7):553-61. doi: 10.1016/S2213-8587(14)70073-7. Epub 2014 May 2. PMID: 24794703.

Which concluded: *Treatment with insulin detemir and aspart in patients with type 1 diabetes and recurrent severe hypoglycaemia resulted in a clinically significant reduced rate of severe hypoglycaemia compared with human insulin. Patients with the greatest chance of benefitting from improved insulin therapy should be offered treatment with insulin analogues and be included in future trials of new insulins.* Note the trial did declare funding from Novo Nordisk A/S.

Second, I believe there has been an over-emphasis on HbA1c in prior analysis of this question at the expensive of other outcomes. HbA1c is rightfully being used as marker of mean blood glucose levels over a prior 90-day period. However, as a marker of mean, frequent hypoglycaemic reactions will pull down an HbA1c. A patient with 6 hypoglycaemic reactions a week vs 1 hypoglycaemic reaction a week may have similar HbA1c but I can assure you the one with 1 hypoglycaemic reaction will be having a greatly improved quality of life. In some high income countries the importance placed on HbA1c is being reduced in favour of time in range and other measures of glycaemia. In addition, the flexibility offered by short-acting insulin analogues is being underappreciated by an HbA1c centric view. Human insulin requires administration well before eating (15-45 minutes before depending on guidance). Short-acting insulin analogues can be taken immediately before eating. This increases quality of life for patients. In short, analysis that places primary emphasis on HbA1c is missing a holistic approach to the question at hand.

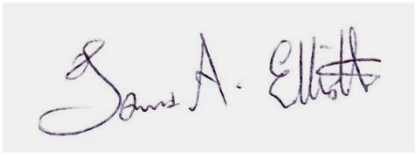
The final reason is equity. When a person in Geneva presents with diabetic ketoacidosis and is newly diagnosed with type 1 diabetes at Hôpitaux Universitaires de Genève (HUG) - are they be started on NPH and regular human insulin? It is extremely unlikely. More than likely, they would be prescribed insulin analogues. Why? Because the superiority of insulin analogues is well understood in high income countries and has been for decades. In high income countries insulin analogues are the mainstay of type 1 diabetes management. Two co-authors and I summarized further equity arguments in a recent publication[1].

JA Elliott, S Ajmal, MTU Barone. 2025. PLOS Global Health Blog Speaking of Medicine and Health. Analogue vs Human Insulin in Low-Income Country Settings: the Debate is Over https://speakingofmedicine.plos.org/2025/03/14/comment-analogue-vs-human-insulin-in-low-income-country-settings-the-debate-is-over/

The price health care systems can acquire rapid-acting insulin analogues can be bargained down through leveraging purchasing power, as the Brazil examples in the above publication demonstrates. The high acquisition price of these agents should not be a reason for keeping off the EML. Indeed, the WHO should redouble efforts to assist Member States in acquiring all forms of diabetes treatment needed to fulfil the global diabetes coverage targets, which include 100% of people with type 1 diabetes have access to affordable insulin and blood glucose self-monitoring.

I believe that for type 1 diabetes treatment, the WHO should be advocating and helping convene stakeholders towards basal/bolus regimes that utilize the best insulin agents available – not just the least expensive or most convenient to acquire from the private sector. This includes short-acting insulin analogues.

Sincerely,



James Andrew Elliott