Comment on Application to Include Long-Acting Insulin Analogues on the WHO Essential Medicines List

Application A20 on Agenda of 23rd WHO Expert Committee on the Selection and Use of Essential Medicines

We would appreciate the attention of the Expert Committee to the following comments on the potential consequences of the inclusion of long-acting insulin analogues on the WHO Essential Medicines List. Those of us who are submitting this comment represent a group of academics and clinicians in the fields of global health, diabetes care, modelling and cost-benefit analysis.

We have been collaborating on a project on costs and benefits of newer medicines for diabetes, including analogue insulins. We have used data from STEPS and related surveys in 67 Low- and Middle-Income Countries to model 10-year outcomes of 25,820 people with diabetes. These outcomes have first been estimated on first-line diabetes treatments recommended in the WHO PEN Guidelines (metformin, gliclazide, human NPH insulin), and then the changes in these outcomes (based on meta-analyses) using the alternatives recommended as treatment in the ADA and EASD Guidelines (SGLT-2 inhibitor, GLP-1 receptor agonist, DPP-4 inhibitor, thiazolidinedione, and analogue insulin glargine). We have used data on drug cost (in 2020 International Dollars, for a given formulation that we converted to a typical dose or per-vial cost to both consumers and any government payers) from the IQVIA MIDAS international drug price database, and estimated costs and disutilities for treatment of diabetes complications, for side-effects and their management, and for equipment and devices associated with treatment (e.g., needles). These models have permitted calculations of incremental costs per Disability-Adjusted Life Years (DALYs) for all included countries of substituting NPH insulin with long-acting analogue insulin among the subset of people who have a history of hypoglycaemia requiring medical attention. We have then calculated the percentage reduction from base price of the drug in each country to reach a common benchmark often used by the World Health Organization for cost-effectiveness, namely having incremental costs per incremental DALY averted (after discounting) be less than three times the GDP per capita.

The median and inter-quartile range of costs for NPH insulin in these 67 countries in 2020 International Dollars is $10 per 10mL vial of 100IU/mL (IQR: $9, $17; mean $13) and for glargine insulin $29 per 10mL vial of 100IU/mL (IQR: $17, $54; mean $37). For analogue insulin, in 42 of the 67 countries, the price is within this 3xGDP per capita range. In 25 countries, however, a reduction in the price of the long-acting analogue would be needed to reach this WHO threshold of cost effectiveness. In 10 countries, this reduction would need to exceed 50% of current price to achieve such a target.

There are further important considerations regarding the situation for insulin availability and affordability in low-income countries and settings.

- Firstly, if long-acting insulin analogues were to be included on the EML, it may important to identify whether manufacturers would be disincentivized from continuing production of human insulin. This in turn would mean that people with diabetes in the countries for which the analogues are above WHO cost-effectiveness thresholds would have no choice but to use it, or more likely would be unable to afford it, which could result in death.
- Secondly, it must be recognised that what is cost-effective is not necessarily affordable for countries or for individuals. Even if analogues were marginally cost-effective in preventing certain complications, the move from human to analogue insulin is likely to increase the absolute cost of insulin around 3-5 times. So, countries currently using human insulin would need to multiply their insulin budget 3- to 5-fold to cater for the same number of patients. The argument is stronger if 50% of diabetes patients in the country do not get insulin at all. Hence inclusion of analogues could make diabetes treatment even less affordable for all of those with diabetes in these countries.
- Finally, it is important to recognise that much of diabetes care in many Low- and Middle-Income Countries is at least in part funded by out-of-pocket expenditure. In these situations, the considerations of benefits across a horizon of 10 years may not be relevant, as the immediate increase in costs may well lead to de-prioritisation of insulin purchasing in order to meet costs of other important components of household expenditure.

We argue that for all these reasons, it is important to consider that the marginal advantages of long-acting analogues collated in a succession of systematic reviews may not warrant the additional costs, either out-of-pocket for people with diabetes or for Ministries of Health.

Signed

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