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Letter in addition to the submission for adding rapid-acting insulin to the WHO's Essential Medicines List re: application A.18 Insulin, analogue rapid-acting – diabetes mellitus

Dear Sirs,

In response to the comments in opposition to the inclusion of rapid acting insulin analogues into the Essential Medication List, I respectfully ask you to consider the following statements.

The texts in bold were copied literally from the WHO NCD department comment.

The recommendation includes both short-acting (regular human insulin – RHI) and intermediate-acting human insulin (NPH insulin). The recommendation is strong because evidence of better effectiveness of insulin analogues is lacking and human insulin has a better resource-use profile. The (weak) recommendation to consider use of insulin analogues to control blood glucose levels in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin has been issued ONLY for long-acting analogues.

Basal insulin analogs have evolved since their introduction to the market in 1999. (Hirsch, Juneja, Beals, Antalys, & Wright, 2020).

Second generation basal analogues (glargine U300, degludec) have demonstrated less documented symptomatic or severe hypoglycemia, even with tight glycemic control, compared to hypoglycemia risk in first generation (detemir, glargine U100) analog users (Meneghini, et al., 2020) - and especially when the results are compared with NPH insulin (Black, Harris, Ryan, Zou, & Ratzki-leewing, 2023), (Rosenstock, Bajaj, Lingway , & Heller, 2024).

They also provide additional benefits, including a more stable and long duration of action, which allows once a day administration and a more flexible injection schedule (Mauricio & Hramiak, 2018)

We conclude the recommendation to use basal analogues is recent, but not weak. We kindly suggest it should be modified, to match current scientific evidence.

Benefits of rapid acting analogues

Initial studies in type 1 diabetes did not demonstrate a significant change in rates of hypoglycemia, but more recent studies show that rapid acting insulin analogues are superior to regular insulin with lower number of total hypoglycemia events, nocturnal and severe hypoglycemia, postprandial glucose and HbA1c (Melo, y otros, 2019).

(Nicolucci, Ceriello, Di Bartolo, Corcos, & Federici, 2020) Evidence demonstrates rapid acting insulin analogues are more effective at reducing postprandial glucose and improving A1c, long- and short-term glucose variability than regular human insulin in type 1 diabetes.

One of the first demonstrated effects of insulin lispro is a 30% lower serum glucose level at one hour and 53% lower at two hours, compared to the effect of regular insulin. This is a statistically significant difference in postprandial glucose control, (Anderson, et al., 1997)

Modern insulin analogues are more predictable, have more consistent absorption rates, are better aligned with the natural insulin production, making glucose control more stable and reliable. They have helped people with diabetes overcome issues like unpredictable absorption, increased risk of hypoglycemia and less flexibility in dosing schedules (Tiwari, Thorat, & Pakale, 2024)

The WHO and rapid acting analogues formulation

The rationale for the development and approval of rapid acting insulin analogues was the need to improve the pharmacokinetic properties of regular insulin to match the postprandial insulin secretion profile in people without diabetes.

This research was proposed by the WHO and the Juvenile Diabetes Foundation in 1985 and led to the development of insulin lispro (1996), then glulisine and aspart. A meta-analysis done in 2006 demonstrated the analogues are superior in terms of causing less severe hypoglycemic episodes in people with type 2 diabetes (Pollock, Valentine, Pilgaard, & Nishimura, 2010). We conclude there is no valid reason for the WHO to oppose the inclusion of rapid acting insulin analogues into the EML.

Summary for effectiveness: The data presented primarily reflect type 1 diabetes, with limited evidence for type 2 or gestational diabetes. The available data do not support the claim of superior effectiveness of insulin analogues over human insulin in improving HbA1c. There are no data on the differences in long-term patient-important outcomes (other adverse events, late complications, mortality).

Summary for adverse effects: The evidence of the risk of hypoglycaemia in people with T1D treated with rapid-acting insulin analogues versus regular human insulin on hypoglycemic events is inconsistent and does not support the claim of the superiority of insulin analogues. Data do not support any difference between rapid-acting insulin analogues versus regular human insulin in people with type 2 diabetes or pregnancy and diabetes

The 2021 consensus report on the management of T1D in adults by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend the use of Ultra Rapid- acting insulin analogs (faster aspart, URAsp; ultra rapid lispro (lispro-aabc), on a level of evidence A, for multiple daily injection in type 2 diabetes, and, in type 1 diabetes, for children and adolescents, for multiple daily injection therapy

and insulin pump use. In type 1 and 2 diabetes, ultra rapid analogues are the level A recommendation for individuals with high postprandial glucose levels (Bowering, Harvey, Kolaczynski, Snyder, & Bode, 2018) (Giorgino, Battelino, & Wilmot, 2023).

We understand expert recommendations do not necessarily have the same level of scientific evidence as randomized controlled trials. Nevertheless, these level A recommendations are based on the best practice standards and are good enough to take evidence-based treatment decisions when scientific evidence is not available, as in this case.

About data for the submission for the treatment of diabetes during pregnancy:

Diabetes during pregnancy has the same treatment goals as diabetes in other stages of life, except that better or tighter control is necessary to ensure fetal and maternal wellbeing. Since there are no adverse effects of basal or rapid insulin analogues on fetal or maternal health, the same recommendations for insulin and diabetes management are valid.

The true question in this debate is, if the international consensus recommends ultra-rapid-acting insulin analogues, why should people with diabetes and their health providers fight for the inclusion of the rapid-acting analogs into the EML? At least the rapid-acting insulin analogues should be included in this list, if not the ultra-rapids as well.

The evidence presented by the applicant is largely derived from studies conducted in type 1 diabetes and does not consistently report benefits across outcomes. The findings cannot be extrapolated to type 2 diabetes, where residual beta-cell function can often meet prandial insulin needs, with exogenous insulin used primarily to address basal insulin deficiency.

Although the pathophysiology of type 1 and type 2 diabetes is different, goals of treatment are the same: goals for glycemic control A1c, Time In Range, Glycemic Variability, and prevention of hypoglycemia and complications in adults are the same in both types of diabetes (American Diabetes Association, 2025).

People with type 2 diabetes who need prandial insulin need to learn to count carbohydrates and need to understand the way their body responds to prandial insulin, in the same way that people with type 1 diabetes do. And healthcare providers must be able to adjust prandial, as well as basal insulin analogues in people with type 2 diabetes.

Mayberry et al (2023) reported that 12.6% of a large cohort of people with type 2 diabetes use only prandial insulin, 6.9% use only basal insulin, and 31.8% were on basal plus prandial insulin. This implies that one out of every three people with type 2 diabetes need prandial insulin to achieve glycemic control. Even if not all people with type 2 diabetes need prandial analogues, these should be available for them, regardless of their type of diabetes. This is not data extrapolation, but the way diabetes medical care and diabetes management – for either type, 1 or 2, or for diabetes due to other causes- should work globally.

A common belief in the medical realm is that adults with type 2 diabetes and end stage renal disease or those who are on renal replacement therapy have lower A1c values and do not need prandial insulin. Recent evidence shows that, especially con hemodialysis days, people with diabetes related end stage renal disease have above-target glycemic variability

indices, which must be addressed to reduce cardiovascular complications (Yusof Khan, Zakaria, Zainal Abidin, & Kamaruddin, 2021).

Since a reported 27% of people with type 2 diabetes have chronic kidney disease (Fenta, Eshetu, Kebede, & et al, 2023), the use and availability of rapid acting analogues should be an integral part of health interventions aimed at reducing diabetes complications.

The belief that people with type 2 diabetes need only basal insulin to achieve glycemic control has been questioned recently with results of continuous glucose monitoring trials (den Braber, et al., 2021) which showed that A1c below 7.0% was not accompanied by the highest Time In Range in people with type 2 diabetes treated with insulin. Also, an A1c >7.9% was not accompanied by less or shorter nocturnal hypoglycemic episodes.

There is well documented scientific evidence to support the goal of achieving better glycemic control in people with type 2 diabetes. For example, a higher glycemic variability is a predictor of disease complications and mortality in people with diabetes requiring hemodialysis (Shi, Liu, Yu, & Han, 2020).

Time In Range is a desired outcome measure for glycemic control (Beck, et al., 2019). Glycemic variability, fasting and postprandial glucose are key components of dysglycemia and must be addressed to reduce the risk of microvascular complications of diabetes (Monnier & Colette, 2008)

The studies presented are disproportionately from high-income countries, where aiming for tighter diabetes control and lower HbA1c levels is more common. The applicability of these findings to low-resource settings, where glucose monitoring is available only to few and achieving lower HbA1c targets is more difficult, should be carefully considered.

The action of "carefully considering" or deciding against the opportunities of people with diabetes in low- and middle-income countries, to achieve a better diabetes management may imply a cognitive or discriminative bias, against which all decision makers should take preventive actions.

Even if continuous glucose monitoring is not available in low- or middle-income countries, the physiology of insulin and diabetes are similar in all the world, since human beings are the same, and respond to insulin in the same way, notwithstanding their socioeconomic status. Evidence on insulin effectiveness, efficacy and safety does not need to be reproduced in every country to be valid.

Income or geographical location must not be a criterion to choose whether a person with diabetes has the right to achieve better or tight glycemic control.

It is true that achieving lower A1c targets is more difficult when insulin, insulin injection and glucose monitoring supplies are not available. In this case, the political decision of not including the rapid acting insulin analogues in the EML can harm people with diabetes, since it broadens the socioeconomic breech in its availability and deprives users of its demonstrated benefits.

So, instead of opposing change, it is very important ensure proper availability of rapid acting insulin analogues and injection supplies, and monitoring devices, since economic

differences should not impact on the lives of people with diabetes, nor should the authorities at the WHO allow this to happen. At this moment, most people with diabetes cannot benefit from insulin analog use because of economic costs.

Respectfully, we call your attention to the fact that a more adequate response from the WHO would include rapid acting insulin analogs, insulin injection supplies and monitoring devices in the EML (see indications for continuous glucose monitoring in type 2 diabetes patients on hemodialysis (Gallieni, et al., 2021)). This measure to include supplies as well is also supported by the American Diabetes Association (2025)

In addition, the pharmacokinetic profiles of bolus and basal insulins are independent of each other and the premise that one being approved supports that the other should be is a void argument.

The pharmacokinetics of basal and prandial analogues is different in the sense that they are designed to simulate pancreatic insulin release. Both types of insulin are not "independent" but complementary.

While using a basal analogue you expect to have a lower prevalence of nocturnal hypoglycemia and a better fasting glucose level. But when using a rapid-acting analogue you expect to improve postprandial glucose levels, improve Time In Range, decrease postprandial excursions, decrease postprandial hypoglycemia, and decrease glucose variability (Hirsch, Juneja, Beals, Antalys, & Wright, 2020).

If you administer a basal analogue with regular human insulin for people on a basal bolus regimen, you will not achieve these prandial benefits. Thus, except for the price matter, it makes no sense to use a basal analogue with regular human insulin for prandial boluses. This is why rapid acting insulin analogues should be included in the EML, as the basal analogues were.

In this document we have proven that the arguments that very few people with type 2 diabetes use prandial insulin, and that most people with type 2 diabetes only use basal insulin are *false.*

High costs of insulin analogues pose a significant barrier in low-resource settings.

Among the barriers for achieving glycemic goals in diabetes management important ones are:

The cost of medications and devices. Skipping, taking less, and/or delaying insulin to save money, i.e., underuse of insulin to save money is termed cost-related medication nonadherence (American Diabetes Association, 2025, p. S18).

Hypoglycemia, hypoglycemia unawareness, and fear of hypoglycemia. The American Diabetes Association (2025, pp. S128-S145) recommends the use of GLP receptor analogues or SGLT- 2 inhibitors to decrease the risk of hypoglycemia in people with type 2 diabetes. Please examine Tables 9.3 and 9.4 and analyze the much higher costs of using these non-insulin medications instead of using insulin analogs. It would be safer and cheaper to use rapid acting insulin analogues than to use these newer medications.

Summary

There is sufficient, good quality evidence to support the fact that rapid acting insulin analogues show a better pharmacological profile for the management of type 1, type 2 diabetes, both in children, adolescents, and adults who use prandial, basal-bolus or continuous insulin infusion regimens.

One of every three adults with type 2 diabetes needs prandial insulin to achieve glycemic control. And one out of every three adults with type 2 diabetes has renal impairment, which, if uncontrolled, may lead to end stage renal disease and the need for renal replacement therapy. In these cases, the use of both basal and rapid acting insulin analogues are a more adequate clinical practice.

Basal and rapid acting insulin analogues are complementary, not independent. To achieve glucose management goals, they must be used together. It is logical to expect approval of the inclusion of rapid acting analogues, since the second-generation basal insulin has been included.

There is a considerable time lag between the release of insulin analogues into the international market and their inclusion in the EML that impacts people with diabetes in low- or middle-income countries in a negative way.

The opposition document seems to suggest that the physiology of diabetes, the pharmacology of insulin, or the treatment goals, are different in higher income settings.

We plead to you, as the authorities responsible for these important health decisions, to analyze the bias in these arguments and make a prompt decision to approve the inclusion of the rapid acting insulin analogues in the EML.

Sincerely,

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