COMMENTS FROM THE DEPARTMENT OF NONCOMMUNICABLE DISEASES, REHABILITATION AND DISABILITY (NCD) ON THE PROPOSAL FOR ADDITION OF RAPID-ACTING INSULIN ANALOGUES (INSULIN LISPRO, INSULIN ASPART, AND INSULIN GLULISINE) TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR THE TREATMENT OF ADULTS WITH TYPE 1 AND TYPE 2 DIABETES MELLITUS AND FOR GESTATIONAL DIABETES AND TO THE ESSENTIAL MEDICINES LIST FOR CHILDREN FOR THE TREATMENT OF TYPE 1 AND TYPE 2 DIABETES

The application was submitted by T1International and was not developed in consultation with the WHO Department of Noncommunicable Diseases, Rehabilitation and Disability.

The technical unit does not support the application to add rapid-acting insulin analogues (insulin lispro, insulin aspart and insulin glulisine) to the 24th WHO Model List of Essential Medicines.

The applications for consideration are:

- insulin lispro 100 IU/mL, 10 mL vial, 3 ml cartridge or pre-filled pen;
- insulin aspart 100 IU/mL, 10 mL vial, 3 mL cartridge or pre-filled pen;
- insulin glulisine 100 IU/mL, 10 mL vial, 3 mL cartridge or pre-filled pen; and
- including biosimilar products.

Target population of the application includes:

- People with type 1 or type 2 diabetes at high risk of experiencing hypoglycaemia with human insulin.
- People with diabetes in pregnancy (gestational diabetes) as defined by the *WHO definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia*

Current WHO recommendations

The *WHO Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus*, published in 2018, recommend short-acting human insulin over analogues for adults with type 1 and type 2 diabetes: "Use human insulin to control blood glucose levels in adults with type 1 diabetes, and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence)." 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.

WHO currently does not have recommendations on pharmacological management of gestational diabetes or pre-existing diabetes in pregnancy.

Effectiveness

- 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. The limited evidence presented for pregnancy and diabetes does not support the claim of its superiority over human insulin.
- 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 section below evaluates the evidence of adverse effects presented in the application:

- Type 1 diabetes:
    - Fullerton (2019 – reference in reference list Fullerton 2016): Cochrane review showing a reduction in HbA1c that is not considered to be clinically meaningful, including by medicines regulatory bodies (-0.15%, 95% CI -0.2% to -0.1%) with insulin analogues.
    - Norgaard (2018): In this systematic review a meta-analysis was only possible for trials comparing human and analogue insulin in continuous subcutaneous insulin infusion (CSII) in children and adults with T1DM. The meta-analysis showed positive outcomes for postprandial glucose control, of unclear benefit. Fasting plasma glucose and HbA1c were compatible with both improvement and worsening.
    - Melo (2019): A systematic review favored insulin analogues for postprandial glucose levels (-1.1 mmol/L) and HbA1c (-0.13%), but these differences do not meet clinically meaningful thresholds (e.g. those used by medicines regulatory bodies such as FDA and EMA).
- Type 2 diabetes:
    - Fullerton (2018): A study on non-pregnant adults with T2DM showed no significant difference in efficacy or harm between insulin analogues and human insulin.
- Diabetes in pregnancy and gestational diabetes:
    - No data on gestational diabetes.
    - O'Neil (2017): This study on pregnancy in T1DM and T2DM suggested no difference in efficacy or harm.
    - Norgaard (2018): In pregnancy with T1DM, the study showed no significant difference in effectiveness.

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).

Adverse effects:

- The adverse effects analysis primarily comes from type 1 diabetes studies with limited data for type 2 diabetes and gestational diabetes. The findings indicate potential benefits for T1D with variability in the statistical significance of these results.

The section below evaluates the evidence of adverse effects presented in the application:

- Type 1 diabetes:
    - Fullerton (2019): Showed a wide confidence interval (0.71 to 1.12) for severe hypoglycaemia, with no significant reduction in hypoglycemic events.
    - Melo (2019): Found reduced number of hypoglycemic events for analogues.
    - Norgaard (2018): The results on the risk of any or severe hypoglycaemia (as well as those on HbA1c) were compatible with both reduced risk and increased risk with analogues, thus not in favour of analogues.
- Type 2 diabetes:
    - Fullerton (2018): A study on non-pregnant adults with T2DM showed no significant difference in efficacy or harms between insulin analogues and human insulin.
- Diabetes in pregnancy and gestational diabetes:
    - No data on gestational diabetes.
    - Norgaard (2018): In pregnancy with T1DM, the results are compatible with both a reduction and an increase in hypoglycaemia with analogues, thus not in favour of analogues.

*Summary for adverse effects: The evidence of the risk of hypoglycaemia in people with T1D treated with r*apid-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 *r*apid-acting insulin analogues versus regular human insulin in people with type 2 diabetes or pregnancy and diabetes.

Affordability

- The applicant suggests that including insulin analogues on the WHO Model List of Essential Medicines (EML) would enable global price negotiations. While production costs for human and analogue insulins are similar, patient costs are not aligned with production costs, the assumption of future price reductions is tenuous. The inclusion of long-acting insulin on the EML on 2021 has not yet resulted in prices even remotely comparable to that of human (NPH) insulin.

- Studies show that analogue insulin remains consistently more expensive than human insulin.
- The report claims that higher acquisition costs may be offset by reduced hospital visits, but it fails to differentiate between insulin access costs and the broader healthcare burden in varying settings. The assumed clinical benefits leading to the reduced hospital visit are speculative as they have not been demonstrated in clinical trials.

The section below evaluates the cost-evidence presented in the application:

- Cost of care:
    - Hall (2003): On type 1 diabetes, found no difference in direct healthcare costs between analogue and human insulin. Analogue insulin incurred higher drug and ambulatory care costs but fewer inpatient hospitalizations. The study does identify that the population is heterogeneous and that people with type 1 diabetes (younger, fewer comorbidities) were the population most likely to be prescribed analogue insulin.

    - Chen (2005): On mixed diabetes populations, found higher pharmaceutical costs for analogue insulin but reduced overall medical costs. Outcomes were influenced by population diversity, with older patients and those with comorbidities more likely to use human insulin.

- Cost-effectiveness:
    - Davey (1998): A willingness-to-pay study in high-income settings found patients willing to pay more for perceived benefits. The applicability of this study to a wider range of healthcare models and the ability to pay for the product is not a robust justification for the inclusion of analogue insulin products.
    - Kilburg (2002): A modelling study on type 1 and type 2 diabetes suggested analogue insulin was cost-effective. However, this modelling study utilised computer modelling from published studies regarding resource use and makes assumptions on the level of diabetes control achieved for patients. The study makes assumptions for theoretical outcomes that have not been demonstrated in clinical trials or real-world evidence. The model is also based upon a specific healthcare model. The theoretical nature of this study calls into question its applicability for the purpose of evaluating cost effectiveness for inclusion in the EML.
    - Reviriego (2008): Found analogue insulin more cost-effective for type 1 diabetes due to fewer severe hypoglycemic events. It is important to note that the study setting, the healthcare system, has a more comparative pricing structure for the access to insulin, with the average cost of analogue insulin quoted at €397 and human insulin €308. This pricing model has not been globally replicated by Ewen et al. (2019).
    - Cameron (2009): Used a modelling that applied a quality-adjusted life year (QALY) approach to the cost effectiveness model based upon the health system standards of the country. The study considered the direct drug costs and the

direct healthcare costs to develop the model. The study concluded that cost-effectiveness varies for the population and that although the use of analogue insulin is associated with a reduction in diabetes related complications, the benefits conferred do not offset the higher acquisition costs for the whole population. The cost-effective analysis in type 1 diabetes met the QALY threshold, however, not for type 2 diabetes and was therefore not cost-effective. The study was undertaken in HIC settings.

- Lloyd (2009): Found analogue insulin cost-effective for pregnant women with type 1 diabetes due to reduced neonatal unit costs, but lacked statistical significance.
- Pratoomsoot (2009): A modelling study on type 1 diabetes in a high-income country favored analogue insulin based on QALY outcomes but acknowledged limited long-term applicability.
- Pollock (2011): A modelling study on type 2 diabetes The study used the trial-generated incidence data for human and analogue insulin benefits and harms and modelled the predicted long-term outcomes. The study favoured analogue for small improvements in life expectancy (note cardiovascular mortality improvement, which for the Japanese study population is not representative of the global picture) and an improvement on QALY.
- Cazarim (2017): A cost-effectiveness study favored human insulin, focusing on direct medicine costs and HbA1c changes.
- Valentine (2018): A modelling study based on a HIC population. The modelling indicates that analogue insulin is cost-effective compared to human insulin, but this study is driven by improvements in QALY related to data on reductions in hypoglycaemia events. The study acknowledged that meta-analysis results have not consistently found a reduction in hypoglycaemic events, and sensitivity analysis to remove the impact of hypoglycaemic events found that analogue insulin is not cost-effective. This study favoured human insulin when taking out trends for reduced hypoglycaemia.
- Nosrati (2023): The study was on T1DM and T2DM and adopted an Iranian healthcare system direct cost approach to assess the cost-effectiveness of insulin products for a 1% change in HbA1c, the incidence of severe hypoglycaemia events and direct drug cost. The study favoured an analogue for type 1 diabetes, but human insulin was favoured for type 2 diabetes. The authors acknowledge that no incremental cost-effectiveness ratio or other willingness-to-pay thresholds were applied to explore the cost-effectiveness.

Summary of affordability: Rapid-acting insulin analogues are more expensive than human insulin. Biosimilars have reduced some costs, but prices remain higher. Cost-effectiveness varies by setting. Potential cost-effectiveness in the modelling of T1D management applied assumptions of clinical benefits that have not been replicated in systematic reviews. Several studies indicated no-cost effectiveness for T1D. No evidence on pregnancy and diabetes was presented. Of the 10 studies of cost-effectiveness, 8 were conducted in high-income countries

and 2 were conducted in upper middle-income countries. At least 6 of the studies were funded and/or authored by insulin manufacturers.

Regulatory consideration

There are no limitations on the regulatory availability of the proposed medicines.

Other considerations

There is a broad statement based upon the rationale of using a rapid-acting analogue in conjunction with the previously approved long-acting insulin analogue preparations. This could be common practice in high-income countries (HIC), where the evidence for each of these components of the T1D insulin regimen was considered separately in the context of the health economic modelling in those countries and does not provide evidence that the combination is superior to alternative combinations. 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.

Conclusion

The evidence presented in the application presents inconsistent evidence and unconvincing arguments for the putative benefits of rapid-acting insulin analogues for type 1 diabetes. Evidence does not support clinical benefits for type 2 diabetes either and the application presents no data for gestational diabetes. High costs of insulin analogues pose a significant barrier in low-resource settings.