A.18 Insulin, analogue rapid-acting – EML and EMLc

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): This Application refers to the addition of **rapid-acting insulin analogues** (Insulin lispro, Insulin aspar, Insulin glulisine) to the WHO Model List of Essential Medicines (EML) for type 1 and type 2 diabetes mellitus (T1DM and T2DM) and gestational diabetes. The evidence summarised in the Application showed a modest benefit over human insulin in terms of the two key outcomes – rate of hypoglycemic events and hemoglobin A1C (HbA1c) levels. The clinical meaningfulness of these differences has been widely debated. Sparse data on health-related quality of life were included, while long-term outcomes such as cardiovascular mortality, progression of nephropathy and retinopathy, end-stage renal disease, lower limb amputation were not assessed in the studies. Clinical trial settings were predominantly high-income countries and data may not be fully transferable to routine health care practice in middle- and low-income settings, where the prevalence of diabetes in steadily increasing. The WHO guidelines for the control of blood glucose levels in non-pregnant adults with diabetes mellitus" currently only recommend the use of human insulin. Rec 4. Insulin. "Use human insulin to manage blood glucose in adults with type 1 diabetes, and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence**)." *This recommendation covers 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* Ref: https://www.who.int/publications/i/item/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 However, rapid-acting insulin analogues can provide more flexibility in administration timing and are largely used and reimbursed in high income countries. Some studies showed evidence of a significantly higher satisfaction scores of people with diabetes treated with short-acting analogue insulin. Moreover, people with T1DM who are prescribed long-acting insulin analogues as background therapy are also prescribed rapid-acting insulin analogues to quickly correct high or rising blood glucose levels before and after meals. Rapid-acting insulin analogues are more expensive than human insulin, but insulin analogues resulted to be cost-effective due to a lower rate of complications, which leads to a reduced demand for high-cost treatments and health care services, especially for T1DM. It should be noted that several cost analyses were funded by the manufacturers of insulin analogues. The availability of rapid-acting analogues along with long-acting analogues may benefit procurement strategies, as they offer greater flexibility in the timing of dosing. The availability of biosimilars may also represent a window of opportunity to decrease procurement prices of insulin analogues. Based on these considerations, this Reviewer supports the inclusion of **rapid-acting insulin analogues**, with insulin lispro as representative of the class and insulin aspart and insulin glulisine included as alternatives (restricted square box). Along with the Committee should encourage efforts in price negotiations and access to biosimilar to help lower costs in the future and decrease significant price disparities.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? **Type 1 and 2 diabetes** Insulins Insulin degludec Insulin detemir Insulin glargine Intermediate-acting insulin	☒ Yes ☐ No ☐ Not applicable

Long-acting insulins (**https://list.essentialmeds.org/**)	
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? The Application reported evidence from six systematic reviews and meta-analyses assessing rapid-acting insulin analogues versus human insulin: <u>Adults with T1DM</u> Fullerton 2019 (9 trials with a total number of 2693 participants) Low certainty evidence for a significant difference in Hba1c of 0.15% (-0.1%; -0.2%), favouring insulin analogues. Risk of (severe) hypoglycemia did not differ between human insulin and insulin analogues (very low certainty of evidence). No data on all-cause mortality, micro and macrovascular complications. <u>Children and adolescents with T1DM</u> Norgaard 2018 (funded by Novo-Nordisk) - five studies in children and adolescents (no difference in the rate of severe hypoglycemia between human insulin and insulin analogues – low quality evidence), - six studies in people on continuous subcutaneous insulin infusion (no difference in fasting glucose level, but a significantly lower postprandial glucose and lower Hba1c, favouring insulin analogues. No significant difference in the risk of hypoglycemia <u>Children and adults with T1DM</u> Melo 2019 (22 trials, with a total number of 6235 participants) - Post-prandial glucose and Hba1c lower with insulin analogues - five studies that assessed quality of life and patient satisfaction (two showed significant results favouring insulin analogues, while three studies did not show any difference) - decreased total and severe hypoglycemic episodes, nocturnal hypoglycemia. In a sensitivity analysis excluding studies with a high risk of bias, there was a significant reduction in the risk of hypoglycemia with insulin analogues by 7%, compared to human insulin <u>Adults with T2DM</u> Fullerton 2018 (10 trials, with a total number of 2751 participants) - no significant difference in all-cause mortality (moderate certainty evidence) and HbA1c (low-certainty evidence) - none of the studies reported on micro or macro-vascular diseases. - no difference in the rate of hypoglycemia (low-certainty evidence) - two trials assessed health-related quality of life and treatment satisfaction, but the results were unreliable (very low-certainty evidence). <u>Pregnant persons with pre-existing diabetes and gestational diabetes mellitus</u> O'Neil 2017, De Jong 2016 Similar results for pregnant persons with pre-existing diabetes and gestational diabetes mellitus.	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? See above data on hypoglycemia	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable

Are there any special requirements for the safe, effective and appropriate use of the medicines? Two companion in vitro diagnostics tests are required for appropriate use of rapid-acting insulin analogues as well as initial diagnosis which also informs the proceeding treatment plan. The two tests are listed on the WHO Model List of Essential In Vitro Diagnostics as Glucose and Haemoglobin A1c (HbA1c)	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? - Two studies conducted in the United States assessed medical costs associated with treatment with human insulin and rapid-acting insulin analogues. Both showed higher pharmacy and office visit costs for insulin analogues but similar total medical costs between the two groups through fewer hospitalizations while delivering health benefits in terms of improved glycemic control. - Ten studies estimated the cost-effectiveness of rapid-acting insulin analogues compared to human insulin for the treatment of T1DM and T2DM. Most of the studies had the perspective of payers from high-income countries**.** In the long term, the total costs of diabetes treatment become similar or even lower with the use of insulin analogues. This is related to a lower rate of complications, which leads to a reduced demand for high-cost treatments and health care services. - Cost-effectiveness studies using Incremental Cost-Effectiveness Ratio (ICER) across various settings demonstrated that rapid-acting insulin analogues can be cost-effective, especially for T1DM. For T2DM, the cost-effectiveness of insulin analogues is more variable with some studies suggesting they may not be as cost-effective for T2DM as for T1DM. Data on gestational diabetes are limited. - Seven articles compared the price of human insulin with that of rapid-acting insulin analogues in different markets, including low- and middle-income countries. Prices of rapid-acting insulin analogues range widely between countries; they are higher than that of human insulin in all the settings, though production cost differences are minimal.	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? Unclear from the Application Regulatory status, approved indications, market availability reported only for high-income countries. Overall, analogue insulins are registered in a smaller number of low- and middle-income countries compared to human insulins. Ref: https://accesstomedicinefoundation.org/medialibrary/221025_atmf-diabetes_access-to-insulin-220903-cmyk-hr.pdf	☐ Yes ☒ No ☐ Not applicable
Does the medicine have wide regulatory approval? Unclear from the Application Regulatory status, approved indications, market availability reported only for high-income countries Overall, analogue insulins are registered in a smaller number of low- and middle-income countries compared to human insulins. Ref: https://accesstomedicinefoundation.org/medialibrary/221025_atmf-diabetes_access-to-insulin-220903-cmyk-hr.pdf	☐ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☒ No ☐ Not applicable