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): For the appropriate management of T1DM rapid-acting insulin analogues are a major need (They must be used in combination with long-acting analogues). The addition of rapid-acting insulin analogues in the EML may have a favorable effect in terms of access.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) SRs and meta-analyses in adults and children with type 1 diabetes, rapid-acting insulin analogues showed a small but statistically significant improvement in HbA1c when compared to NPH (Fullerton 2016, Nogaard 2018, Melo 2019). No difference was seen on mortality, CV complications of quality of life (Fullerton 2016). For T2DM gestational no difference was seen in HbA1c or mortality (Fullerton 2018). Similar results were seen in patients with gestational diabetes and pregnant patients with pre-gestational diabetes. Overall, the evidence is low to moderate quality due to biases and heterogeneity, but findings were consistent across multiple studies,	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) There is adequate evidence to support the safety profile of rapid-acting insulin analogues for the proposed use. No increased harms compared to human insulin. Evidence suggests that rapid-acting analogues may slightly reduce the risk of hypoglycemia when compared to human insulin. Additionally**,** it seems to be a safe option during pregnancy (as safe as human insulin) It is important to highlight there is limited safety data in very young children	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? Based on the available evidence, rapid-acting insulin demonstrates a favorable and meaningful balance of benefits to harms for the treatment of type 1 and type 2 diabetes mellitus, as well as gestational diabetes.	☒ Yes ☐ No ☐ Not applicable

They present similar glycemic control (with minimal additional benefit in postprandial glucose management and Hb A1c) with a reduced risk of severe and nocturnal hypoglycemia compared to human insulin. No unexpected safety concerns were identified, and the known adverse effects, such as hypoglycemia and weight gain, are consistent with the established profile of insulin therapies and are manageable with appropriate clinical oversight.	
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) • Patients must be trained in glucose monitoring as well as insulin storage, administration and dose calculation (including glucose monitoring). Additionally, education on recognizing and managing hypoglycemia is essential. • Appropriate health care personnel are required	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? Rapid-acting insulin analogues are generally more expensive than human insulin. This is mainly secondary to market dominance by a few manufacturers (costs of production are only slightly higher). Cost effectiveness analyses have show**n** that rapid acting analogues may be cost-effective in the long-term due to reduced complications (such as fewer hospitalizations for hypoglycemia. On the other, they may be cost effective in T2Dm when compared to NPH.	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes) Rapid-acting insulin analogues are widely available in HICs. They are usually accessible through national healthcare systems or insurance coverage. On the other hand, in LMICs access is limited due to high prices, lack of insurance coverage, weak procurement systems, and limited biosimilar competition.	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval? Rapid-acting insulin analogues are widely approved by major regulatory agencies worldwide**.**	☒ Yes, for the proposed indication. ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable