A.20	Long Acting Insulin Analogues
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Currently, diabetes affected an estimated 463 million people in 2019, or 9.3% of the global population, of which 79% live in low- and middle-income countries.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	EML includes human insulins (regular and NPH) that are used for the same purposes.
Have all important studies and all relevant evidence been included in the application?	☐ Yes ☒ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: The systematic review developed by Monami el at. Included RCTs that compared long-acting insulin analogues (detemir or glargine) with NPH insulin in type 2 diabetic for >12 weeks. It concluded that long-acting insulin analogues in type 2 diabetic patients does not provide a better glycemic control in comparison with NPH insulin, whereas they reduced the risk of nocturnal and symptomatic hypoglycaemia [1].
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). Laranjeira 2018 and Tricco 2018 compared long acting analogues vs. NPH in patients with type 1 diabetes. • Laranjeira 2018 reported that long-acting insulin analogues led to a reduction in general hypoglycaemia (RR 0.95, 95%CI 0.91-0.99), nocturnal hypoglycaemia episodes (RR 0.66, 95%CI 0.57–0.76) as well as a reduction in HbA1c (mean difference -0.17, 95%CI -0.23 – 0.12). There was no significant difference on severe hypoglycaemia. As we can see most outcomes show minimal reduction, whether this leads to clinically significant improvement is unknown. • Tricco 2021 showed similar results. Long acting analogues demostrated a statistically significant superiority in the following outcomes: major or serious hypoglycaemic episodes, and nocturnal hypoglycaemic episodes. No significant difference for all hypoglycaemic events. In this review there was no difference in terms of clinical complications (vascular complications, microvascular complications or macrovascular complications0. Also no

	difference in any adverse events, serious adverse events and drop-outs due to adverse events Almeida evaluated the impact of glargine on quality of life in patients with type 1 diabetes. It favoured glargine over NPH. The metrics with significant differences tended to be 'satisfaction with treatment' or 'perception of hyperglycaemia . Semlitsch 2020 , is a systematic review that compared long-acting analogues glargine and detemir vs. NPH in patients with type 2 diabetes. Meta-analysis found no significant differences in severe hypoglycaemic events, HbA1c, all-cause mortality, diabetes-related complications, or adverse events other than hypoglycaemia. Lv 2015 evaluated pregnant women with pre gestational diabetes. Long acting analogues were not associated with additional benefits on fetal/ neonatal outcomes
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Laranjeira 2018: • General hypoglycaemia (RR 0.95, 95%CI 0.91-0.99), • Nocturnal hypoglycaemia episodes (RR 0.66, 95%CI 0.57–0.76) • No significant difference for severe hypoglycaemia Tricco 2021: • Insulin analogues did not show to decrease all hypoglycaemic events • Insulin analogues were associated with decreased the risk of nocturnal hypoglycaemia. Determir and Glargine decreased major or serious events but this was not the case for deglucedec Cherubini 2019, is a systematic review that evaluated the risk of severe hypoglycaemic events in pediatric patients with type 1 diabetes. It found 2 observational studies with conflicting results. On the other hand, Hemmingsen 2021 found that insulin determir was associated with decreased risk of severe hypoglycaemia (adults and children with type 1 diabetes); this was not the case for glargine. Additionally, glargine and determinir did not decrease the risk of severe nocturnal hypoglycaemia Semlitsch 2020 did not find difference in severe hypoglycaemic events or other adverse events in patients with type 2 diabetes. On the other hand, analogues showed to decreased the following outcomes: • Serious hypoglycaemia ((determir only, not glargine), • Confirmed hypoglycaemia <75 mg/dL (determir only, not glargine), hypoglycaemia, 55mlg/dL • Confirmed nocturnal hypoglycaemia <75mg/dL and <55ng/dL Czech 2015 (systematic review of observational studies) did not find no significant difference in the rate of severe hypoglycaemic evens with biphasic human insulin compared to biphasic insulin analogue in patients with type and type 2 diabetes.

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Patients receiving insulin need frequent monitoring for hypo/hyperglycaemia and their consequences
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	I consider the profile of insulin analogues is favourable
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Moderate. I consider there are multiple well-conducted studies evaluating the effect of the insulin analogues. Unfortunately, most of them evaluate their impact in adult population; children with type 1 diabetes may have additional benefits not as relevant not considered in these studies. Also, most studies present limited follow up times limiting our ability to conclude about their impact on complication since it can take years for them to develop.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: The administration of insulin requires training. To achieve adequate control frequent blood sugar measures are necessary. Patient and caregivers need to be prepared and trained for the management of potential hypoglycaemia. This is a requirement for all types of insulin.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:

Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	In this case cost is a significant limitation to access insulin analogues. According to ACCISS 2017 report the prices of insulin vary significantly: For government procurement, the median price for 1000 units of analogue insulin was USD34.20 compared to US$5.99 for human insulin. When bought by patients from public sector facilities, median price for analogue insulin was USD45.03 compared to US$7.64 for human insulin. When bought by patients in the private sector, median price for long-acting insulin analogues was USD39.35 compared to USD16.65 for human insulin.(
Any additional comments	
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	Insulin analogues seem to have a slightly better profile when compared to intermediate acting insulin. They showed minimal advantage on glucose control but no impact on patient important outcomes such as mortality, vascular complications. This could be related to short follow up periods. It is important to highlight that there seems to be a reduction in the development of hypoglycemic events (particularly relevant for pediatric population). Insulin analogues have not shown significant superiority over NPH and considering a substantial price difference I believe that their inclusion in the EML isn't justified.
References (if required)	1. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract. 2008 Aug;81(2):184-9. doi: 10.1016/j.diabres.2008.04.007. Epub 2008 May 20. PMID: 18495286.