(1) **Does the application adequately address the issue of the public health need for the medicine?**

Yes ☐  No ☐

Please provide brief details:

Diabetes mellitus is a common disease worldwide, type 1 diabetes (T1DM) accounts for 5-10% of all cases. The incidence of T1DM is on the rise, with reported increases between 2-5% per year in Europe, the Middle East, Australia and the United States \(^1\)\(^3\). The most affected seem to be young children. If these trends were to continue, the number of new cases of T1DM in children younger than five years of age is expected to double in some regions between 2005 and 2020, and to rise by 70 percent for prevalent cases in children under 15 years \(^3\). The reasons behind these trends are unknown.

Patients with T1DM and 10% of patients with T2M require insulin therapy. Unfortunately, lack of access due to cost is a major problem, which could lead to severe complications, long-term disability and even death. Access to insulin compared to other non-communicable disease medications was found to be 2.5 to 45 times higher priced.

(2) **Have all-important studies/evidence of which you are aware been included in the application?**

Yes ☐  No ☐

Please provide brief comments on any relevant studies that have not been included:

NA

(3) **Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?**

Yes ☐  No ☐

(a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine:
Presented evidence is based on well-conducted systematic review and network meta-analysis evaluating 68 studies. This review found a statistically significant benefit of long acting insulin over intermediate acting insulin in the following surrogate outcomes:

- **Glycated haemoglobin:** MD -0.15 (-0.21 to -0.07). Human and biosimilar long-acting insulin were statistically significantly better than human intermediate acting insulin.
- **Fasting plasma glucose:** MD -1.03 (-1.33 to -0.73). Results were consistent for biosimilar and human long acting insulin. For this outcome, ultra-long acting was also better than intermediate acting insulin; MD -1.45 (-2.12 to -0.79)
- **Weight change:** MD -0.70 (-1.07 to -0.33). In this case long-acting human seemed to be slightly better than biosimilar.

It is difficult to determine whether these differences would be reflected in a clinically significant effect.

No statistically significant differences were seen for mortality, vascular complications (microvascular, macrovascular or total) or quality of life. Short follow up periods (0.14 to 104.36 weeks) may not allow us to appreciate an impact of these outcomes.

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:

Yes, the included studies were developed in South America, Africa, Asia, Australia North America and Europe (most of them). Unfortunately, children were not evaluated.

(4) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes  □  No  □

Please provide brief details:

Presented evidence is based on well-conducted systematic review and network meta-analysis evaluating 68 studies. This review found a statistically significant benefit of long acting insulin over intermediate acting insulin in the following outcomes:

- **Serious Hypoglycaemia:** OR 0.63 (0.51-0.76). Results were consistent for human and biosimilar long-acting insulin
- **Nocturnal Hypoglycaemia:** OR 0.71 (0.57-0.89). Ultra-long acting insulin also showed statistically significant advantage over intermediate acting insulin OR 0.60 (0.42-0.86).
  - Additionally intermediate acting human insulin BID showed to increased the odds of nocturnal hypoglycaemia when compared to ultra-long-acting biosimilar od
No statistically significant differences were seen for all-cause hypoglycaemia and minor/mild hypoglycaemia, adverse events (serious adverse events, dropouts due to adverse events and any adverse events) or incidence of cancer.

(5) Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).

Long acting insulins (human or biosimilar) seem to have a slightly better profile when compared to intermediate acting insulin. They showed a small advantage on HbA1C, fasting plasma glucose and weight. They were unable to show benefit on patient important outcomes such as mortality, vascular complications and quality of life. This could be related to short follow up periods. It is important to highlight that they showed reduction in the development of serious hypoglycaemia and nocturnal hypoglycaemia, which are important and potentially deadly adverse events. This is particularly important in paediatric population that may not be able to recognize and/or communicate signs and symptoms of hypoglycaemia. This makes long-acting insulin a safer option. Considering their decreased risk of hypoglycaemia and the previously exposed biochemical benefits, long-acting insulin appears as the best option for the management of patient with T1DM.
ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☐ No ☐

Please provide brief details:

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.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐ No ☐

Please provide brief details:

Long-acting insulin analogues are licensed will believe with a indication of treatment of diabetes mellitus in adults, adolescents and children two years and older.

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☐ No ☐

Please provide brief details:

Not to my knowledge.
Of note, long-acting insulins were included as part of the “Guidelines for the prevention, management and care of diabetes mellitus “ developed by WHO Eastern Mediterranean regional office published on 2006

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

The annual cost of insulin was estimated at $736 per patient in 2013, which had triplicate is from 2002. Please 2014 the prices insulin has increased by 64%. Additionally, a recent analysis on 22 insulin brands show that manufactures are still racing insulin prices, and costs now vary by as much as 10 times depending on the insulin type. Bio similar insulins have the potential to reduce treatment costs leading to improved access for patients and healthcare systems.

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Any additional comments?

No

Please frame the decisions and recommendations that the Expert Committee could make.

Based on the presented evidence long-acting insulin appears to be slightly more effective and safer than intermediate-acting insulin for the management of T1DM.

References (if required)


