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

Yes  X  No  

Please provide brief details:

Type 1 diabetes is a global issue and affects a significant proportion of the population. Adequate treatment for individuals, that will reduce the impact of the disease on their quality of life and on the life-threatening and quality of life-compromising complications of the disease are warranted. The application accurately addresses this issue in adults. The use in children and adolescents is not addressed.

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

Yes  X  No  X

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

The data pertains studies in adults with T1DM. As such, to my knowledge, it is thorough, complete and unbiased.

On the other hand, it is likely that the paediatric population would also benefit from long-acting insulins. Indeed, T1DM (i) often begins in childhood, (ii) it is harder to maintain glycemic control in children and adolescents; and (iii) it is likely that it is in children that we may observe the largest effect size.

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

Yes  X  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:

The application provides data on two surrogate markers as primary end-points: A1c and fasting plasma glucose. The importance of glycemic control to avoid long-term consequences of diabetes is a correct assumption and therefore these two end-points are appropriate surrogates in the context. For these surrogate end-points, for which there is a considerable amount of studies that can be included, long-acting insulins fairled better than intermediate-acting insulins. Secondary outcomes, which correspond to hard outcomes, were also evaluated: mortality, vascular complications, microvascular and macrovascular complications and
quality of life. For these, a reduced number of studies could be retrieved or used. Although data was not sufficient to form a final judgement, no statistical differences were found between long-acting and intermediate-acting insulins, which are already listed.

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

N/A

(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 X No □

Please provide brief details:
The application has evaluated adverse effects in comparison to intermediate-acting insulins, which are already listed, finding no differences. The safety profile has also been evaluated concentrating on hypoglycemias. Long-acting insulins appeared superior to intermediate-acting insulins for serious hypoglycemias, although all cause-hypoglycemias did not appear different.

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

Overall, the risk/benefit of long-acting insulins is positive.
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 prescription of insulins should be performed by a healthcare professional competent in diabetes care and the patient and family should be adequately trained in self-administration and in the management of common side effects, such as hypoglycemias. This is similar to insulin and intermediate-acting insulins, which are already listed in the EML.

(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:
The medicines under evaluation have a different regulatory history and have been on the market for different times. Yet, the protocols for authorization all rely mainly on glycemic control and A1c levels.

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

Yes ☐ No ☒

- 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 –

The guideline favours in low-resource settings the use of intermediate-acting insulins based on cost and the lack of reliable and consistent data that shows superiority of one insulin over another. The guideline therefore does not contradict the inclusion in the EML of long-acting insulins as long as intermediate-acting insulins are maintained.

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

Cost and affordability are an obvious issue for recombinant proteins, in light of the presumably higher production cost compared to small molecules and on the limited amount of producers. Insulins pose a further problem, as the prevalence of T1DM might have a significant budget impact. Yet, the inclusion of valid alternatives and the recent advent of biosimilars should reduce this risk. Recent European experiences have shown that the advent of biosimilars for therapeutic proteins has significantly reduced the cost for the prevalent population. Last, it should be noticed that the half-life of recombinant proteins should not correlate with cost.
(10) Any additional comments?

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

a. Recommend the inclusion of long-acting insulin analogues as a pharmacological class in the EML to the core list for T1DM in adults.

b. Have a square box for long-acting insulins.

c. Consider long-acting analogues as an OR category to intermediate-acting insulin. Indeed, this would further strengthen competition in the insulin field.

c. Do not de-list intermediate-acting insulins. Indeed, while superiority is likely in glycemic control as measured by surrogate outcomes, there is insufficient data to affirm conclusively that a large effect size difference is seen on hard-outcomes.

d. Consider drugs for T1DM and T2DM diabetes as an area to concentrate in the future to update the list in both children and adults and to promote biosimilar development in this area.

(12) References (if required)