### Long-acting insulin analogues

**Indication**: Type 1 diabetes mellitus

**ICD11 code**: 5A10

**Medicine type**: Biological agent

**List type**: Core

**Additional notes**: Including quality-assured biosimilars

**Formulations**: Parenteral > General injections > SC: 100 IU per mL in 3 mL cartridge; 100 IU per mL in 3 mL pre-filled syringe

**EML status history**: First added in 2021

**Sex**: All

**Age**: Also recommended for children

**Therapeutic alternatives**: Medicines within the same pharmacological class can be used

**Patent information**: Patents have expired in most jurisdictions

**Tags**: Biosimilar

**Wikipedia**: Long-acting insulin analogues

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**Expert Committee recommendation**

The Expert Committee once again acknowledged that insulin is a life-saving essential medicines for which a strong public health need exists, and equitable and affordable access to insulin globally is still a challenge. The Committee also recalled that the price difference between human insulin and insulin analogues, relative to the magnitude of benefit of insulin analogues, has been the primary reason for the Committee not recommending listing insulin analogues on many occasions in the past. In its current consideration, the Committee noted that the magnitude of the benefit of insulin degludec, detemir and glargine over human insulin in terms of reduced glycated haemoglobin (a surrogate marker highly correlated with clinical outcomes) remains modest. However, the Committee considered that evidence for an advantage of long-acting insulin analogues over human insulin with regard to a lower incidence of symptomatic and nocturnal hypoglycaemia was consistent and clinically relevant, particularly in the subset of patients with type 1 diabetes who have frequent severe hypoglycaemia (requiring assistance) with human insulin. In type 2 diabetes, the frequency of severe hypoglycaemia is generally lower than in type 1 diabetes, thus the differences in the rates of hypoglycaemia and severe hypoglycaemia between long-acting analogues and human insulin may be more limited. However, the Committee noted that people with type 2 diabetes with long-lasting insulin deficiency can develop an insulin-dependent disease similar to type 1 diabetes. In these people, the frequency of hypoglycaemia events with human insulin progressively rises, potentially leading to more pronounced benefits of insulin analogues. The Committee noted that the benefits in terms of reduced hypoglycaemia of different insulin analogues may vary. However, there is currently limited evidence of clear superiority of one analogue over another. The Committee noted the absence of data from settings with food insecurity where insulin analogues may have greater theoretical advantages, and the lack of experimental studies comparing the long-term outcomes of insulin analogues and human insulin, for example, diabetic complications (nephropathy) or mortality. With regard to price, the Committee noted that national markets differ considerably in the insulin prices offered to patients and procurers and that insulin analogues are still generally much more expensive than human insulin. However, overall use of insulin analogues is expanding and prices have decreased for insulin analogues that are no longer under patent protection in some markets. In settings where cost-containment...
actions and efficient procurement negotiations are in place, prices of insulin analogues are aligning with those of human insulin. The Committee acknowledged that the listing of insulin analogues as alternatives to human insulin may result in a higher proportion of expensive analogue insulins being used, which could have serious implications for affordability for both individuals and health systems. The Committee recommended that the inclusion of insulin analogues in national reimbursement schemes should be planned carefully and be complemented with dedicated cost-containment policies. The Committee noted and shared the concerns expressed by several stakeholders about potential effects of the inclusion of insulin analogues on the Model Lists on the human insulin market, currently dominated by three pharmaceutical companies, and the financial implications for patients and health systems where insulin analogues are not available or affordable. The Committee was unequivocal that access to affordable human insulin remains a critical priority, globally. The Committee noted that the efforts made by the WHO Prequalification Unit to prequalify human insulin had not been successful, possibly because of a lack of interest by manufacturers of human insulin, but that interest from manufacturers to prequalify insulin analogues had emerged. The Committee noted that, while vials have an important role in hospitals, at the community level, prefilled disposable insulin pens and reusable insulin pens with disposable insulin cartridges are preferable. The Committee also noted that access to devices to monitor blood glucose levels is often limited and should be addressed together with interventions to improve access to insulin and injection devices. Taking all these factors into consideration, the Expert Committee decided to recommend inclusion of long-acting insulin analogues on the core list of the EML and EMLc for the treatment of patients with type 1 or type 2 diabetes mellitus who are at high risk of experiencing hypoglycaemia with human insulin. The Committee considered that this recommendation was adequately supported by the available evidence and is aligned with the recommendation in the WHO guidelines. However, the recommendation did not receive the support of all Committee members, mainly due to concerns about the differences in price and potential effect on the availability of human insulin. A square box listing was recommended, with therapeutic alternatives limited to insulin degludec, insulin detemir and insulin glargine. The Committee also recommended that quality-assured biosimilars were acceptable alternatives based on evidence of therapeutic equivalence and safety of switching to biosimilars from the reference products. Switching and substitution of reference insulins with biosimilars could result in considerable savings at the country level, with increased access to medicines associated with favourable outcomes. The Committee noted that the inclusion of long-acting insulin analogues on the Model Lists could facilitate the WHO prequalification process and recommended that insulin analogues be considered for inclusion in the call for expressions of interest for WHO prequalification. The Committee recognized the current high price of insulins, both human and analogues, as a barrier to access. The Committee considered that this barrier could be removed or mitigated through multiple actions, including price negotiations, pooled procurement, competitive tendering, support of technology transfer between manufacturers and the increased use of biosimilars. The Committee recommended WHO to continue working on policies and actions that will lead to relevant and rapid price reductions at the country level, based on systematic evaluation of evidence and implementation experiences of countries. The Committee encourages WHO to evaluate the effect of the EML listing of insulin analogues on the global availability, accessibility and price of insulins over a multiyear period. The Committee also highlighted the importance of commitment and action from Member States, insulin producers, procurement agencies and other stakeholders to address the problem of equitable and affordable access to insulin products globally. The Committee also considered that insulins could be a priority medicine for the proposed Working Group on high-priced essential medicines. The Working Group, in close coordination with the WHO pricing team, should develop a specific approach to determine fair-price thresholds at the country level for insulins and insulin devices (e.g. pens) and diagnostics (e.g. glucometers), recognizing the valuable role WHO can play in monitoring and defining fair prices, facilitating access and supporting progress towards universal health coverage.