Long-acting insulin analogues

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.

### Background

Long-acting insulin analogues were previously considered by the Expert Committee in 2013, 2017 and 2019 (1–3). Insulin analogues are medicines whose molecular structure is similar to endogenous human insulin, a 51-amino acid polypeptide. Human insulin is available in various forms, as (regular) insulin with a rapid onset of action, slow-acting neutral protamine Hagedorn (NPH) insulin or zinc-based preparations. Insulin analogues were designed to mimic physiological insulin profiles more closely than human insulin injections, which is relevant especially for people with type 1 diabetes who are more at risk of frequent and severe hypoglycaemia events. Insulin analogues can be classified based on their duration of action. The long-acting insulin analogues insulin glargine and insulin degludec were designed to provide more stable basal insulin-action profiles and longer coverage of
Worldwide, diabetes affected an estimated 463 million people in 2019 (9.3% of the global population), of whom 79% live in low- and middle-income countries (4). The number of people with diabetes has almost tripled in the past 3 decades due to: increase in population size; population ageing; and the increasing prevalence of the main risk factors for diabetes – overweight, obesity and physical inactivity (5). In 2019, diabetes was responsible for over 1.5 million deaths and 2.79% of all global disability-adjusted life years (6). The burden of diabetes is projected to increase to affect 700 million people in 2045 (7). Diabetes is estimated to reduce life expectancy by 6 years when diagnosed at 40 years (8), and is a major cause of peripheral neuropathy, blindness, kidney failure and lower limb amputation. Diabetes complications affect quality of life and often lead to premature deaths, which is experienced by about a half of all people with diabetes. The incidence and prevalence of type 2 diabetes are much higher than type 1 diabetes, with type 2 diabetes responsible for about 90–95% of all diabetes cases (4). The annual global expenditure on health care for people with diabetes is estimated to be US$ 850 billion, 12% of the overall global health care expenditure (7). All people with type 1 diabetes have an absolute need for insulin for survival. A proportion of people with type 2 diabetes (less than 10%) also need insulin at some point in the course of their disease (9).

**Public health relevance**

Type 1 diabetes A 2018 meta-analysis including 28 randomized controlled trials found that, compared with human NPH insulin (an insulin with intermediate duration of action), long-acting insulin analogues led to a significant reduction in general hypoglycaemia (relative risk (RR) 0.95, 95% confidence interval (CI) 0.91 to 0.99), nocturnal hypoglycaemia episodes (RR 0.66, 95% CI 0.57 to 0.76) and haemoglobin A1c (HbA1c) – mean difference (MD) –0.17, 95% CI –0.23 to –0.12. No significant difference was observed for severe hypoglycaemia (RR 0.94, 95% CI 0.71 to 1.24) (10). A 2021 systematic review and network meta-analysis of 64 randomized controlled trials and one non-randomized controlled trial compared long-acting insulin analogues and biosimilars with human insulin in adults with type 1 diabetes (11). The risk of bias varied for different elements (unclear in most trials for the random sequence generation, allocation concealment and selective reporting; high in most trials for the blinding of participants and personnel and other biases). The network meta-analysis found that long-acting insulin analogues led to fewer major or serious hypoglycaemia episodes (odds ratio (OR) 0.63, 95% CI 0.51 to 0.79) and nocturnal hypoglycaemia episodes (OR 0.74, 95% CI 0.58 to 0.94), and reductions in HbA1c (MD –0.14 percentage points (95% CI –0.22 to –0.06), fasting plasma glucose (MD –1.03 mmol/L (95% CI –1.33 to –0.73 mmol/L) and weight (MD –0.7 kg (95% CI –1.08 to –0.32 kg). No significant differences were found for all-cause hypoglycaemia, vascular complications, microvascular complications, macrovascular complications, any adverse events, serious adverse events and drop-outs due to adverse events (11). A systematic review of eight studies (four randomized controlled trials and four cohort studies) evaluated quality of life outcomes with insulin glargine compared with human NPH insulin (12). Five studies reported statistically significant differences in quality of life, favouring glargine over NPH insulin, in certain areas. One study did not report on quality of life outcomes, and two reported no statistically significant difference in any of the variables measured. Where insulin glargine was significantly better in quality of life measures, differences were in the areas of satisfaction with treatment or perception of hyperglycaemia. A systematic review of severe hypoglycaemia in paediatric patients with type 1 diabetes, including two real-world observational studies, compared long-acting insulin analogues and human NPH insulin and had inconclusive findings (13). The review noted a temporal trend showing marked reduction in the incidence of severe hypoglycaemia since 1993, which the authors proposed could be associated with increased use of new insulin therapies and related devices and diagnostics. One of the included analyses of 2025 patients found a significantly lower incidence rate ratio of 0.46 (95% CI 0.22 to
Harms

Refer to benefits section.

Additional evidence

0.95) for serious hypoglycaemia with long-acting insulin analogues compared with NPH insulin (14). In another analysis (7266 patients), hypoglycaemia episodes were significantly more common in patients using long-acting insulin analogues than in patients using NPH insulin (OR 1.57, 95% CI 1.21 to 2.03). These episodes included situations that required attention to prevent glucose levels dropping further and situations in which children experienced some impaired awareness. The increased risk for severe hypoglycaemia episodes requiring external assistance was not statistically significant (OR 1.42, 95% CI 0.86 to 2.35) (15). A Cochrane systematic review comparing long-term treatment with (ultra-)long-acting insulin analogues with NPH insulin included 26 randomized controlled trials in adults and children (8784 participants) which had a follow-up duration of at least 24 week (16). Insulin detemir was associated with a significantly lower risk of severe hypoglycaemia events than NPH insulin (RR 0.69, 95% CI 0.52 to 0.92 (eight studies, 3219 participants; moderate-certainty evidence)). No significant difference was found between insulin glargine and NPH insulin in their effect on severe hypoglycaemia events (RR 0.84, 95% CI 0.67 to 1.04 (nine studies, 2350 participants; moderate-certainty evidence)). The review did not explore a pharmacological class effect for long-acting analogues, and combined results across detemir trials and glargine trials. Results were uncertain for severe nocturnal hypoglycaemia for both detemir and glargine. Few data were available on mortality and other important outcomes for patients. The meta-analysis found no significant difference in HbA1c between insulin detemir and NPH insulin (MD 0.01%, 95% CI –0.1 to 0.1% (eight studies, 3122 participants; moderate-certainty evidence)), or between insulin glargine and NPH insulin (MD 0.02%, 95% –0.1 to 0.1% (nine studies; 2285 participants)). Type 2 diabetes A 2020 Cochrane review comparing (ultra-)long-acting insulin analogues with NPH insulin included 24 randomized controlled trials in adults with type 2 diabetes. The review found a significant reduction in certain measures of hypoglycaemia for insulin glargine or insulin detemir compared with NPH insulin, but no significant differences in severe hypoglycaemia events, HbA1c, all-cause mortality, diabetes-related complications, or adverse events other than hypoglycaemia (17). The review did not explore a pharmacological class effect for long-acting analogues, and combined results across detemir trials and glargine trials. For health-related quality of life, three trials reported no statistically significant difference between insulin glargine and NPH insulin. The other three trials reported no statistically significant difference between insulin detemir and NPH insulin. The authors noted that, overall, the included studies used very low blood glucose/HbA1c target values; the findings may therefore be less applicable for patient groups where less aggressive glycaemic targets are used (e.g. elderly people). Pooled analysis of type 1 and 2 diabetes A 2015 systematic review of 76 observational studies evaluated the risk of severe hypoglycaemia in patients with type 1 and 2 diabetes as observed in everyday clinical practice for various drug regimens (18). In type 1 diabetes, the estimated annual probability of one or more severe hypoglycaemia event per patient varied from 21.4% (95% CI 11.3% to 43.0%) for basal-bolus routine with insulin analogues to 33.8% (95% CI 17.9% to 67.5%) for basal-bolus routine with human insulin. Differences for type 2 diabetes were more pronounced: the estimated annual probability of one or more severe hypoglycaemia event per patient varied from 4.8% (95% CI 1.2% to 27.0%) for basal-bolus routine with insulin analogues to 33.8% (95% CI 17.9% to 67.5%) for basal-bolus routine with human insulin. Differences were minimal when basal therapy was combined with oral antidiabetic medication. Another systematic review and meta-analysis of 23 studies compared insulin analogues with human insulin in hospitalized adults with type 1 or 2 diabetes. Outcomes included hyperglycaemia episodes, surgical site infection, postoperative complications, length of hospital stay and mortality (19). Comparing analogue basal-bolus routine regimens with human insulin basal-bolus regimens, a meta-analysis of four randomized trials estimated that analogues reduced days spent in hospital by 0.9 days (95% CI –1.45 to –0.34 days), with low quality of evidence. One randomized controlled trial found lower rates of postoperative complications (RR 0.69, 95% CI 0.52 to 0.93) with very low quality of evidence. Two randomized controlled trials and one cohort study compared long-acting insulin analogues with human NPH insulin in hospitalized patients. The cohort study (in 172 hospitalized patients undergoing major surgery) found a reduction in hypoglycaemia events (very low-quality evidence), while the randomized trials were inconclusive. A 2015 systematic review identified eight observational studies comparing insulin glargine with NPH insulin, and one observational study and one randomized controlled trial comparing insulin detemir with NPH insulin in patients with (pre-)gestational diabetes (20). A meta-analysis of these studies found no significant differences in fetal, neonatal or maternal outcomes. Similarly, a meta-analysis found no significant differences in fetal/neonatal or maternal outcomes for insulin detemir. With regard to biosimilars, evidence to date indicates no safety signals when switching patients from originator to biosimilar insulin (21).
Some authors have studied the potential risk of developing different types of cancer with medicines used to manage diabetes, including long-acting insulin analogues. A 2013 systematic review and meta-analysis evaluated the cancer risk associated with insulin use from experimental and observational studies (22). Insulin glargine exposure was found to be associated with an increased risk of cancer in the pancreas (RR 2.58, 95% CI 2.05 to 3.25), liver (RR 1.84, 95% CI 1.32 to 2.58), kidney (RR 1.38, 95% CI 1.06 to 1.79), stomach (RR 1.65, 95% CI 1.02 to 2.68) and respiratory system (RR 1.30, 95% CI 1.14 to 1.47), and decreased risk of prostate cancer (RR 0.80, 95% CI 0.73 to 0.88). Insulin glargine exposure was associated with a decreased risk of colon cancer (RR 0.71, 95% CI 0.56 to 0.91) and a marginally significant increased risk of breast cancer (RR 1.14, 95% CI 1.01 to 1.29) compared with users of non-glargine insulin. The results from individual studies were very variable and for most cancers there were few cases, calling into question the certainty of the findings. Two meta-analyses of data from randomized controlled trials from manufacturer’s pharmacovigilance databases evaluated the role of insulin in the generation of cancers. When insulin glargine was compared with any active comparator (insulin or oral antidiabetics), there were slightly fewer cancer cases in the glargine arm but the difference was not statistically significant (RR 0.90, 95% CI 0.60 to 1.36) (23). The second meta-analysis compared insulin detemir with NPH insulin and found more cases of cancer in the NPH insulin arm (OR 2.44 95% CI 1.01 to 5.89) (24).

Cost / cost effectiveness

There are long-standing concerns about the prices of long-acting insulin analogues, which are substantially higher than prices of human insulins in most comparisons. This is of particular concern given the broader crisis in global access to insulin therapy in general, where an estimated one in two people who need insulin cannot afford it (26). The application notes that the price reductions for analogue insulins and biosimilars has fallen since the 2019 application. Most available cost–effectiveness studies focus on high-income settings. In all studies, procurement costs for long-acting insulin analogues are considerably greater than for human insulins. Some cost–effectiveness analyses have found that, despite greater procurement cost, insulin analogues are more cost-effective than human insulins because of savings resulting from (assumed/modelled) health benefits such as lower rates of hypoglycaemia. A systematic review of the cost–effectiveness of insulin analogue included 50 studies, of which 33 focused on type 2 diabetes, 11 on type 1 diabetes, and six on both type 1 and type 2 diabetes (27). Twenty-one studies compared long-acting insulin analogues with NPH insulin, all of which were from high-income countries. Long-acting insulin analogues were dominant over NPH insulin in five comparisons (i.e. had both lower cost and greater benefits) and were dominated by NPH in one comparison (i.e. had both greater cost and lesser benefits). Apart from these cases, the incremental cost–effectiveness ratios for long-acting insulin analogues compared to insulin NPH ranged from US$ 661 to US$ 361 721 per quality adjusted life year (QALY). This large range in the incremental cost–effectiveness ratios is caused by different underlying assumptions used across studies, particularly regarding: (i) the baseline characteristics of patients, complication frequency and severity, use and cost of self-monitoring blood glucose test strips and devices (e.g. pen, cartridge, vial), and (ii) the different (estimated) magnitudes of benefit in reducing hypoglycaemia events and reductions in HbA1c. Six cost–effectiveness studies of long-acting insulin analogues published between 2015 and 2020 were identified in the application (28–33). Long-acting insulin analogues were found to be cost-effective compared to human insulins in several studies in Asia. In France, insulin glargine was cost–effective but not insulin detemir. Neither was cost-effective in a study within the Brazilian health system. A study in China assessed insulin cost in wages and found that a month’s supply of long-acting insulin analogues cost 14–16 days’ wages for the lowest-paid government worker compared with 4–7 days for other insulins. In their most recent report (2017), the Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS) study gave insulin prices from a range of sources, including: government procurement prices in 26 countries, the Gulf Cooperation Council and the United Nations Relief and Works Agency for Palestine Refugees; prices paid by patients (solicited from respondents in 43 countries); and reimbursement prices collected from publicly accessible databases for 28 countries (34).

For government procurement, the median price for 1000 units of long-acting insulin analogues was US$ 34.20 compared with US$ 5.99 for human insulin. When bought by patients from public-sector facilities, the median price of 1000 units for long-acting insulin analogues was US$ 45.03 compared with US$ 7.64 for human insulin. When bought by patients in the private sector, the median price for long-acting insulin analogues was US$ 39.35 compared with US$ 16.65 for human insulin. A report on recent trends in insulin prices submitted to the 2021 Expert Committee highlighted that in many countries, access to long-acting insulin analogues is limited and hampered by the higher costs compared with human insulin (35). The report states that “Overall, there is great variability among countries regarding the price of and access to long-acting insulin analogues, often still much more expensive than human insulin. However, overall use on analogues seems to be expanding and prices decreasing at least for those insulins that are not anymore patent protected”. The report also summarizes procurement prices in most WHO regions. Countries that are more
likely to reach best insulin prices are those that have adopted insulin price control policies and/or where contract negotiations are supported by competition laws. In these countries, human insulin pen prices can vary between US$ 2 and US$ 5, while analogues pen can vary between US$ 5 and US$ 10. These trends are also reported in other studies. For instance, in Bangladesh, biosimilars of long-acting insulin analogues supported by dedicated policy actions on pharmaceutical cost, cost about the same as human insulin and represent an increasing market share (36). The additional benefit of long-acting insulin analogues in formulations of higher concentrations (300 units/mL versus 100 units/mL) is still unclear and could be a so-called evergreening strategy (extending the life-time of patents about to expire to retain royalties). These higher-concentration products account for increasing large market shares, even though their prices are unlikely to be reduced, as they are under active patent protection (35). The authors of the current application suggest that the EML should be forward-looking and have a reasonable expectation that a product’s price will substantially decrease in the near-to-medium-term (e.g. 5 years), particularly if policy approaches favour biosimilars and cost-containment is pursued at the country level. They noted that, “EML listing can serve as a helpful signal to manufacturers of what medicines may benefit the most from generic/biosimilar market entry, as well as a signal to governments as to where interventions in the market are necessary to increase competition or cap prices”. The application also highlights that if long-acting insulins are added to the WHO Model Lists, it is important that individual governments do not interpret this as a recommendation for a wholesale switch from human to analogue insulins, but that long-acting insulins should be included as alternatives. In parallel, countries need to work with manufacturers and other stakeholders to support the availability of human insulin, even in a period in which the use of human insulin is likely to decline.

The 2018 WHO guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes (25) include the following recommendations. • Use human insulin to control blood glucose levels in adults with type 1 diabetes and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence). • Consider long-acting insulin analogues to control blood glucose levels in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (weak recommendation, moderate-quality evidence for severe hypoglycaemia). The second recommendation is weak, “reflecting the lack of, or very low-quality evidence for, any of the long-term outcomes such as chronic diabetes complications and mortality, and the considerable higher costs for long-acting insulin analogues compared to intermediate-acting human insulin”

Most patents have expired for nearly all insulin analogues (with the exception of formulations with higher concentration of 300 IU/mL), although intellectual property barriers remain in some cases for insulin injection devices (37,38). At present, there are no manufacturers of prequalified active pharmaceutical ingredient for insulin or finished pharmaceutical products (39,40). In 2019, WHO started a pilot project for prequalification of human insulin products, including human insulin, and invited manufacturers to submit an expression of interest (41). However, to date, no insulin manufacturers have submitted dossiers for prequalification. There may be many reasons for this apparent lack of interest, for example: (i) being an old, low-cost but also low-profit product, few manufacturers still produce human insulin and the market is dominated by a small number of market leaders who may have little incentive to submit for prequalification; (ii) smaller companies with an established local market may not have ambitions beyond the local market because of costs and regulatory resources; and (iii) manufacturers may not be interested in complying with WHO good manufacturing practice or in investing in improving the product or willing to enter into the commitments that inevitably come with prequalification (variations, reinspections, requalification etc.). Over the past 2 years, the WHO Prequalification Unit has had the opportunity to exchange information with companies that produce insulin. From this dialogue, interest by manufacturers in a prequalification process that could cover more types of insulin has emerged. Supporting multisourcing tender strategies and accelerating the introduction of multiple types of insulin biosimilars can boost competition. This should include not only the type of insulin itself but also the device used for administration. WHO’s prequalification of insulin/devices is a valuable tool to: enhance cooperation between regulators and manufacturers; expand the number of producers of quality-assured insulins and associated devices; and tackle access to insulins in low- and middle-income countries. Including insulin analogues and single-use prefilled syringes/pens as essential medicines can stimulate submissions of dossiers for prequalification from manufacturers.


23. Home PD, Lagarennne P. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. Diabet


