World Health Organization

REGIONAL OFFICE FOR **Europe**

Consideration of diabetes medicines as part of the revisions to 2019 WHO Model List of Essential Medicines for adults (EML)

Long-acting insulin analogues: Insulin glargine; Insulin detemir; Insulin degludec (and biosimilars)

This summary has been prepared by the Health Technologies and Pharmaceuticals (HTP) programme at the WHO Regional Office for Europe.

It is intended to communicate changes to the WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc) to national counterparts involved in the evidence-based selection of medicines for inclusion in national essential medicines lists (NEMLs), lists of medicines for inclusion in reimbursement programs, and medicine formularies for use in primary, secondary and tertiary care.

This document does not replace the full report of the WHO Expert Committee on Selection and Use of Essential Medicines (see The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021). Licence: CC BY-NC-SA 3.0 IGO: https://apps.who.int/iris/bitstream/handle/10665/330668/9789241210300-eng.pdf?ua=1) and Corrigenda (March 2020) – TRS1021 (https://www.who.int/medicines/publications/essentialmedicines/TRS1021_corrigenda_March2020.pdf?ua=1).

Executive summary of the report: https://apps.who.int/iris/bitstream/handle/10665/325773/WHO-MVP-EMP-IAU-2019.05-eng.pdf?ua=1.

The revised lists of essential medicines are available here:

-        World Health Organization Model List of Essential Medicines, 21st List, 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO (https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1).

-        World Health Organization Model List of Essential Medicines for Children, 7th List, 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO (https://apps.who.int/iris/bitstream/handle/10665/325772/WHO-MVP-EMP-IAU-2019.07-eng.pdf?ua=1).

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Section 18: Medicines for endocrine disorders

18.5 Insulin and other medicines used for diabetes

Rejected application for addition of long-acting insulin analogues (including biosimilars) to EML

Insulin detemir (ATC Code A10AE05); Insulin glargine (ATC Code A10AE04); Insulin degludec (ATC Code A10AE06)

Background

Human insulin has been included on the EML since the first list in 1977 (1). In 1985, the WHO Expert Committee on the Selection and Use of Essential Medicines approved the inclusion of isophane neutral protamine Hagedorn (NPH) insulin (2).

Since 1996, different insulin analogues, altered form of human insulins, have been introduced on markets worldwide. Over the last years additional comparative evidence on biosimilars and reference medications in terms of efficacy and safety became available.

In 2017, at the 21st meeting of the Expert Committee of the WHO EML, an application for the inclusion of long-acting analogues to the EML was rejected due to the limited magnitude of the benefits of analogues over human insulin in terms of reduced glycated haemoglobin and reduced hypoglycaemia as compared to the large difference in price between analogues and human insulin (3).

Since that time, additional evidence has become available encompassing both effectiveness and increasing affordability of analogues.

Public health relevance

Diabetes mellitus has an increasing worldwide prevalence. If current trends continue, it is estimated that 642 million adults will be living with diabetes by 2040 (4). The incidence of type 1 diabetes mellitus (T1DM) accounts for a small proportion of all diabetes (range: 5-10%) (5).

All people living with type 1 diabetes have an absolute need for insulin for survival. Insulin is also required by a subset of patients with type 2 diabetes (6). Lack of access to affordable insulin is a problem globally and contributes to the complications of untreated or sub-optimally treated diabetes and premature deaths (7).

Application

The application proposed the addition of long-acting insulin analogues as a pharmacological class to the core list of the EML for the treatment of patients with type 1 diabetes (T1DM) with a square box listing.

Scientific evidence of benefits and harms

Benefits

The application presented the findings of a network meta-analysis (NMA) to evaluate the comparative effectiveness and safety of long- or intermediate-acting insulin versus biosimilar insulins in patients with T1DM, updating the results of a previous systematic review.

The review compared basal regimens and categorizes treatments as per class of basal insulin (i.e. intermediate acting, long-acting and ultra-long-acting), and specific type of basal insulin, including insulin origin and insulin frequency. The analyses were adjusted for bolus regimen.

Sixty-eight primary studies (8-75) (and 12 companion reports) involving 15,150 patients with average age ranging from 23 to 54 years were included. Sixty-two (91%) studies were RCTs and the majority had an unclear/high risk of bias on random sequence generation, allocation concealment, selective reporting, and "other' bias (e.g., funding bias). Details of the included studies are available in Appendix File 1 of the application at:
https://www.who.int/selection_medicines/committees/expert/22/applications/s18.5_insulin-analogues.pdf?ua=1.

Primary efficacy outcomes of the network meta-analysis were A1c and fasting plasma glucose. Secondary efficacy outcomes were mortality, any (total) vascular complication, microvascular complications, macrovascular complications and quality of life.

A1c

A basal insulin class NMA was conducted including 26 RCTs and 9,241 patients and 3 treatment nodes (long-acting, intermediate-acting, and ultra-long-acting biosimilar). Long-acting insulin was statistically superior to intermediate-acting insulin (mean difference MD -0.14, 95% confidence interval CI: -0.21 to -0.07).

A specific type of insulin NMA was conducted on the A1c outcome including 34 RCTs and 11,894 patients and 9 treatment nodes. Across the 36 treatment comparisons, the following 11 showed statistically significant results:

- Intermediate-acting (human) insulin administered four times a day (qid) was *inferior* to intermediate-acting (animal and human) insulin administered twice a day (bd) (mean difference MD 0.31, 95% confidence interval CI: 0.05 to 0.57)

- Intermediate-acting (human) insulin administered qid was *inferior* to intermediate-acting (human) insulin administered bid (MD 0.43, 95% CI: 0.23 to 0.63)

- Intermediate-acting (human) insulin administered qid was *inferior* to intermediate-acting (human) insulin administered once daily (od) (MD 0.32, 95% CI: 0.10 to 0.53)

- Long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered qid (MD -0.46, 95% CI -0.67 to -0.24)

- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered qid (MD -0.49, 95% CI -0.70 to -0.29)

- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered od (MD -0.18, 95% CI -0.30 to -0.06)

- Long-acting (human) insulin administered od was *superior* to intermediate-acting (animal and human) insulin administered bid (MD -0.19, 95% CI -0.37 to -0.01)

- Long-acting (human) insulin administered od was *superior* to intermediate-acting (animal) insulin administered bid (MD -1.27, 95% CI -2.54 to -0.01)

- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered qid (MD -0.50, 95% CI -0.69 to -0.31)

- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered od (MD -0.18, 95% CI -0.29 to -0.08)

- Ultra-long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered qid (MD -0.44, 95% CI -0.64 to -0.23).

A sensitivity analysis to examine the impact of imputing missing standard deviations on the results resulted in the exclusion of seven trials. The pairwise treatment comparisons above were no longer statistically significant when the seven trials were excluded.

When meta-regression analyses were conducted for follow-up duration, A1c level (mild: <8%, severe: ≥8%); proportion of women; duration of diabetes, and risk of bias associated with random sequence generation and allocation concealment; none of the results remained statistically significant.

Statistically significant results were shown for meta-regression analyses on:

- bolus type (rapid versus short): long-acting (human) insulin administered od was *superior* to intermediate-acting (animal) insulin administered bid (MD -1.27, 95% CI: -2.54 to -0.001)

- study design (parallel or cross-over trials): long-acting (human) insulin administered bid was *superior* to intermediate-acting (animal) insulin administered bid (MD -1.27, 95% CI: -2.53 to -0.0007)

- baseline A1c: intermediate-acting (animal and human) insulin administered bid was superior to intermediate-acting (animal) insulin administered bid (MD -1.32, 95% CI: -2.63 to -0.02)

- age: long-acting (human) insulin administered bid, was superior to intermediate-acting (animal) insulin administered bid (MD -1.31, 95% CI: -2.58 to -0.04) and long-acting (human) insulin administered od was superior to intermediate-acting (animal) insulin administered bid (MD -1.28, 95% CI: -2.54 to -0.007.

Fasting plasma glucose

A basal insulin class NMA was conducted on the fasting plasma glucose outcome including 21 RCTs, 7,685 patients, and 3 treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (MD -1.03, 95% CI: -1.33 to -0.73) and ultra-long-acting insulin was superior to intermediate-acting insulin (MD -1.45, 95% CI: -2.12 to -0.79).

A specific type of insulin NMA was conducted on the fasting plasma glucose outcome including 28 RCTs, 9,773 patients, and 8 treatment nodes. Across the 28 treatment comparisons, the following nine showed statistically significant results:

- Long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered bid (MD -1.07, 95% CI: -1.98 to -0.15)

- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered bid (MD -0.82, 95% CI: -1.21 to -0.43)

- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered bid (MD -1.26, 95% CI: -1.66 to -0.85)

- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered od (MD -1.15, 95% CI: -1.82 to -0.49)

- Long-acting (human) insulin administered od was *superior* to long-acting (human) bid (MD -0.43, 95% CI: -0.82 to -0.05)

- Ultra-long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered qid (MD -1.20, 95% CI: -2.31 to -0.09)

- Ultra-long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) bid (MD -1.55, 95% CI: -2.24 to -0.87)

- Ultra-long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered od (MD -1.45, 95% CI: -2.34 to -0.56)

- Ultra-long-acting (biosimilar) insulin administered od was *superior* to long-acting (human) insulin administered bid (MD -0.73, 95% CI -1.38 to -0.08).

Mortality

A NMA was not possible for all-cause mortality for basal insulin classes. Two pairwise meta-analyses were possible for long-acting versus intermediate-acting insulin (4 RCTs, 1682 patients), as well as ultra-long-acting versus long-acting insulin (2 RCTs, 1540 patients). None of the results were statistically significant.

A NMA was not possible for all-cause mortality for specific types of insulin. Three pairwise meta-analyses were possible comparing long-acting (human) insulin administered bid versus intermediate-acting (human) insulin administered bid (2 RCTs, 653 patients), long-acting (human) insulin administered od versus long-acting (biosimilar) insulin administered od (2 RCTs, 1093 patients) and long-acting (human) insulin administered od versus ultra-long-acting (biosimilar) insulin administered od (2 RCTs, 1540 patients). None of the results were statistically significant.

Any (total) vascular complication

A basal insulin class NMA was conducted on any vascular complication, including 11 RCTs and 4,709 patients. Across the 3 treatment comparisons, none were statistically significant.

A specific type of insulin NMA was conducted on any vascular complication including 13 RCTs and 5,589 patients. Across the 10 treatment comparisons, none were statistically significant.

Microvascular complications

A basal insulin class NMA was conducted to compare long-acting, intermediate-acting and ultra-long acting insulins on microvascular complications including 8 RCTs and 3,131 patients. The transitivity assumption was upheld but inconsistency could not be assessed since there were no closed loops in the network meta-analysis diagram. Across the 3 treatment comparisons, none were statistically significant.

A specific type of insulin NMA was conducted on microvascular complications including 10 RCTs and 4,011 patients. Across the 10 treatment comparisons, none were statistically significant.

Macrovascular complications

For basal insulin classes, a NMA was not possible for macrovascular complications. Two pairwise meta-analyses were possible; long-acting insulin versus intermediate-acting insulin (3 RCTs, 998 patients) and ultra-long-acting biosimilar insulin versus long-acting insulin (3 RCTs, 2,098 patients). The results of pairwise treatment comparisons were not statistically significant.

For specific types of insulin, a NMA was not possible for macrovascular complications. Two pairwise meta-analyses were possible for long-acting (human) insulin administered bid versus intermediate-acting (human) insulin administered bid (4 RCTs, 1258 patients) and long-acting (human) insulin administered od versus ultra-long-acting (biosimilar) od (2 RCTs, 1540 patients). The results were not statistically significant.

Quality of life

A NMA or pairwise meta-analyses were not possible for health-related quality of life for basal insulin classes or specific types of insulin. One study including 517 patients reported total quality of life and long-acting (human) insulin administered od was not statistically significant compared with intermediate-acting (human) insulin administered bid. The same study reported general quality of life and long-acting (human) insulin administered od was not statistically significant compared with intermediate-acting (human) insulin administered bid. With respect to basal insulin classes, similar results were observed when long-acting insulin was compared to intermediate-acting insulin.

Harms

Weight change

A basal insulin class NMA was conducted including 16 RCTs, 6,822 patients, and 3 treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (MD -0.70, 95% CI: -1.07 to -0.33).

A specific type of insulin NMA was conducted including 20 RCTs, 8,335 patients, and 7 treatment nodes. Across the 21 treatment comparisons, the following four showed statistically significant results:

- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered bid (MD -0.85, 95% CI: -1.24 to -0.46)

- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered od (MD -1.18, 95% CI: -2.13 to -0.24)

- Long-acting (human) insulin administered bid was *superior* to long-acting (biosimilar) insulin administered od (MD -0.96, 95% CI: -1.91 to -0.01)

- Long-acting (human) insulin administered bid was superior to ultra-long-acting (biosimilar) insulin administered od (MD -0.69, 95% CI: -1.32 to -0.06).

All-cause hypoglycaemia (defined differently across RCTs)

A basal insulin class NMA was conducted including 17 RCTs and 5,949 patients. Across the 3 treatment comparisons, none were statistically significant.

A specific type of insulin NMA was conducted including 22 RCTs and 6,917 patients. Across the 21 treatment comparisons, none were statistically significant.

Major or serious hypoglycaemia (defined differently across RCTs)

A basal insulin class NMA was conducted including 19 RCTs, 7324 patients, and 3 treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (odds ratio OR 0.63, 95% CI: 0.51 to 0.76).

A specific type of insulin NMA was conducted including 25 RCTs and 9,300 patients. Across the 21 treatment comparisons, the following four showed statistically significant results:

- Long-acting (biosimilar) insulin administered od was *superior* to intermediate-acting (human) insulin administered bid (odds ratio OR 0.48, 95% CI: 0.24 to 0.97)

- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered bid (OR 0.69, 95% CI: 0.54 to 0.88)

- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered bid (OR 0.53, 95% CI: 0.39 to 0.72)

- Long-acting (human) insulin administered od was *superior* to intermediate-acting (human) insulin administered od (OR 0.60, 95% CI: 0.42 to 0.86).

Minor or mild hypoglycemia

For basal insulin classes, a NMA was not possible. One pairwise meta-analysis was possible for long-acting versus intermediate-acting insulin (8 RCTs, 2,949 patients) and the results were not statistically significant.

A specific type of insulin NMA was conducted including 11 RCTs and 3,926 patients. Across the 15 treatment comparisons, none were statistically significant.

Nocturnal hypoglycemia (defined differently across RCTs)

A basal insulin class NMA was conducted including 16 RCTs, 6,669 patients, and 3 treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (OR 0.71, 95% CI: 0.57 to 0.89) and ultra-long-acting biosimilar insulin was statistically superior to intermediate-acting insulin (OR 0.60, 95% CI: 0.42 to 0.86).

A specific type of insulin NMA was conducted including 19 RCTs and 7,564 patients. Across the 15 treatment comparisons, the following two showed statistically significant results:

- Intermediate-acting (human) insulin administered bid was *inferior* to ultra-long-acting (biosimilar) insulin administered od (OR 1.58, 95% CI: 1.11 to 2.25)
- Long-acting (human) insulin administered bid was *superior* to intermediate-acting (human) insulin administered bid (OR 0.59, 95% CI: 0.44 to 0.79).

Incident cancers

For basal insulin classes, a NMA was not possible. One pairwise meta-analysis was possible for long-acting versus intermediate-acting insulin (3 RCTs, 1,651 patients) and the results were not statistically significant.

For specific types of insulin, a NMA was not possible. One pairwise meta-analysis was possible (2 RCTs and 1204 patients), which compared long-acting (human) insulin administered od versus intermediate-acting (human) insulin administered bid. The results were not statistically significant.

Any (total) adverse events, serious adverse events, and dropouts due to adverse events

For basal insulin classes, NMAs were conducted on any adverse events including 16 RCTs and 5,367 patients, on serious adverse events including 20 RCTs and 6,840 patients, and on withdrawals due to adverse events including 14 RCTs and 5,440 patients. Across the 3 treatment comparisons in each NMA, none were statistically significant.

For specific types of insulin, NMAs were conducted on any adverse events including 22 RCTs and 6,830 patients, on serious adverse events including 26 RCTs and 8,989 patients, and on withdrawals due to adverse events including 21 RCTs and 7,795 patients. Across the 15 treatment comparisons in each NMA, none were statistically significant.

Other considerations

The review found long-acting insulin analogues to be superior to intermediate-acting insulin with regard to major or serious hypoglycaemia, which may represent an advantage particularly in settings where food security is not reliable. Glucagon, used in the management of severe hypoglycaemia, has very limited availability in many low-resource settings (89). Thus, the lower incidence of major or serious hypoglycemias associated with the use of (ultra) long-acting insulin analogues may offer further advantages in such settings.

The Committee acknowledged and noted the comments received in relation to this application from organizations and individuals expressing concern about the potential inclusion of insulin analogues on the Model List and associated consequences.

WHO Guidelines

WHO's 2018 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 (84) make the following recommendations regarding the use of insulin:

- use human insulin (short-acting regular human insulin and intermediate-acting human insulin (NPH insulin)) to manage blood glucose 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 manage blood glucose in adults with type 1 or type 2 diabetes who have frequent severe hypoglycemia with human insulin (weak recommendation, moderate-quality evidence for severe hypoglycemia).

Recommendations from the 2018 WHO's guidelines targeting type 1 diabetes were based on evidence from systematic reviews of randomized controlled trials (85-87).

For patients with type 1 diabetes, the mean difference in HbA1c level between short-acting insulin analogues and regular human insulin was −0.15% (95 CI −0.20% to −0.10%) (*low-quality evidence*). The difference in HbA1c level in patients treated with short-acting insulin analogues compared with those treated with regular human insulin was not considered clinically meaningful by the guidelines development group. Long-acting insulin analogues and human NPH insulin had similar effects on HbA1c level (*moderate-quality evidence*). Long acting insulin analogues reduced risk for severe hypoglycemia, but only the reduction with detemir was statistically significant (*moderate-quality evidence*). The guideline panel concluded that the relatively modest overall benefit from insulin analogues was outweighed by the large price difference between human insulin and insulin analogues. Thus, the panel considered use of long-acting detemir and glargine insulin analogues as an alternative to human insulin only in specific circumstances, such as unexplained and frequent severe hypoglycemic events.

Expert Committee recommendations

The Committee acknowledged that insulin is a life-saving essential medicine for which a compelling public health need exists. Yet despite being available for almost 100 years, achieving reliable, equitable and affordable access to insulin remains a public health challenge in many countries.

The Committee did not recommend the addition of insulin analogues to the EML, reiterating the conclusion of the 2017 Expert Committee, that while long-acting insulin analogues are an effective treatment for type 1 diabetes, the available evidence shows efficacy and safety advantages of analogues compared to human insulin which are insufficiently large to justify the cost differential that continues to exist in most settings.

The Committee remained concerned about the ongoing problems of access and affordability of insulin worldwide, despite human insulin not being patented. The Committee noted the long-standing domination of the insulin market by three manufacturers, limiting broader competition and slowing the entry of biosimilars to the market.

Recognizing the complexities of these problems and the need for a wider understanding of the insulin market and access to insulin, the Committee recommended WHO coordinate a series of actions to address the issues of insulin access and affordability. In the absence of other coordinated actions, the Committee considered that the inclusion of insulin analogues for adults on the EML would be inadequate to address the underlying issues of poor access and affordability of insulins more generally.

The Committee recommended that a WHO-led approach should be multi-factorial and multi-disciplinary and should include:

- establishment of an independent WHO technical working group on access to insulin;

- consultation with Member States and other stakeholders to identify/clarify barriers to access at country level;

- strategies to address current regulatory barriers for biosimilar insulins, such as the expansion of the WHO Prequalification Programme;

- development of a comprehensive approach to address insulin prices, including mechanisms for pooled procurement;

- identification of evidence and research gaps regarding insulin use and supply, including setting-specific differences in clinical practice and health systems (e.g., food insecurity, displaced populations, emergencies).

The Committee would welcome a report that comprehensively describes the actions that are undertaken by WHO over the next biennium and an application that reviews more in depth current challenges for optimal global access and the role of insulin analogues in children.

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