Insulin (analogue, rapid-acting)

Essential medicine status

ATC codes: A10AB05 A10AB06 A10AB04

Indication	Type 2 diabetes mellitus ICD11 code: 5A11
Medicine type	Biological agent
List type	Core
Formulations	Parenteral > General injections > SC: 100 IU per 1 mL in 10 mL vial ; 100 IU per 1 mL in 3 mL cartridge ; 100 IU per 1 mL in 3 mL pre-filled pen
EML status history	First added in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	insulin lispro (ATC codes: A10AB04) Parenteral > General injections > SC: 100 IU per mL in 10 mL vial; 100 IU per mL in 3 mL cartridge; 100 IU per mL in 3 mL pre-filled pen insulin aspart (ATC codes: A10AB05) Parenteral > General injections > SC: 100 IU per mL in 10 mL vial; 100 IU per mL in 3 mL cartridge; 100 IU per mL in 3 mL pre-filled pen insulin glulisine (ATC codes: A10AB06) Parenteral > General injections > SC: 100 IU per mL in 10 mL vial; 100 IU per mL in 3 mL cartridge; 100 IU per mL in 3 mL pre-filled pen
Patent information	Read more about patents.
Wikipedia	Insulin (analogue, rapid-acting)

Expert Committee recommendation

The Expert Committee recognized the importance of affordable and equitable access to insulin products as a public health priority. The Committee considered that the available evidence indicates generally comparable efficacy and safety between rapid-acting insulin analogues and regular human insulin. The Committee noted that some studies provided evidence of higher patient satisfaction scores with rapid-acting insulin analogues and others suggest that rapid-acting insulin analogues may be associated with lower rates of complications, with medicine costs offset by reduced demand for high-cost treatments and health services for complications, particularly in type 1 diabetes. However, the Committee considered these benefits were tenuous and did not provide compelling arguments to support the inclusion of rapid-acting insulin analogues on the Model Lists. The Committee recognized that rapid-acting insulin analogues may be more expensive than regular human insulin and may be less affordable in some resource-constrained settings. However, in other settings the prices of rapid-acting insulin analogues do not exceed the price of regular human insulin. The Committee noted that larger insulin markets could help stabilize prices, secure supply chains of quality-assured products and mitigate the risks of shortages. In countries where insulin prices are excessive, consideration should be given to strengthening the regulatory framework, implementing or maintaining price control, or reference-pricing mechanisms. The outcomes of price controls and reference pricing for essential medicines should be closely monitored as these policies can have unintended consequences, e.g. shortages. The Committee emphasized the importance of commitment and action from WHO, Member States, insulin producers, procurement agencies and other stakeholders to address the problem of equitable and affordable access to insulin products globally. The Committee highlighted the need for multipronged policy, pricing and procurement strategies to strengthen affordable access. In consideration of access to insulin, the Committee noted with concern the progressive withdrawal of regular human insulin from markets. The Committee acknowledged the concerns of the WHO technical department that the inclusion of rapid-acting insulin analogues might adversely affect the ongoing availability of regular human insulin, particularly in the most resource-constrained settings. However, the Committee also noted that in the case of insulin, EML-listing was unlikely to be the strongest or most influential driver of market access nor to revive the marginal sales of

human insulin. The Committee emphasized that no changes were being made to the status of human insulins on the Model Lists. The Committee considered that the inclusion of rapid-acting insulin analogues would serve to increase the number of insulin products on the Model Lists and would complement the listing of long-acting insulin analogues for use in basal-bolus regimens. This is consistent with the listings for short- and intermediate-acting human insulins. Based on these considerations, the Expert Committee recommended the inclusion of rapid-acting insulin analogues (insulin aspart, insulin glulisine and insulin lispro, and their quality-assured biosimilars, as therapeutic alternatives) on the core list of the EML and EMLc for the treatment of people with type 1 and type 2 diabetes, and people with gestational diabetes.

Background

Rapid-acting insulin analogues have not previously been evaluated for inclusion on the Model Lists. The Model Lists currently include human insulin (short- and intermediate-acting) and long-acting insulin analogues.

Public health relevance

The public health relevance of insulin in the treatment of diabetes is well established. According to data from the Global Burden of Disease study, diabetes mellitus affected 525.6 million people globally in 2021. Most cases were type 2 diabetes (506 million). The disease was responsible for more than 1.6 million deaths and 2.7% of global disability-adjusted life years (1). A 2021 study estimated the global prevalence of gestational diabetes to be 14.0% (2).

Benefits

Type 1 diabetes A 2016 Cochrane systematic review of nine randomized controlled trials (2693 participants) assessed the effects of rapid-acting insulin analogues versus regular human insulin in non-pregnant adults with type 1 diabetes (3). Six studies involved insulin lispro and three studies involved insulin aspart. For the secondary outcome of glycaemic control, the mean difference (MD) in glycated haemoglobin (HbA1c) favoured rapid-acting insulin analogues (MD −0.15% (95% confidence interval (CI) −0.21% to −0.08%; nine randomized controlled trials, 2608 participants; low-quality evidence). No data on all-cause mortality or micro- and macrovascular complications were reported in the trials. A 2018 systematic review and meta-analysis assessed the efficacy and safety rapid-acting insulin analogues in children and adolescents (five randomized controlled trials) and people using continuous subcutaneous insulin infusion (six randomized controlled trials) with type 1 diabetes (4). The review also identified seven randomized controlled trials in pregnancy, but these were not included in the quantitative meta-analysis due to heterogeneity. Among children and adolescent trials, no significant difference was found between rapid-acting insulin analogues and regular human insulin for severe hypoglycaemic events (risk difference (RD) 0.00, 95% CI −0.01 to 0.01; five randomized controlled trials, 1216 participants). Among the trials on continuous subcutaneous insulin infusion, rapid-acting insulin analogues led to greater lowering of postprandial plasma glucose than regular human insulin (MD −1.63 mmol/L, 95% CI −1.71 to −1.54 mmol/L,; five randomized controlled trials, 460 participants), but no significant differences were found between treatment groups for fasting plasma glucose (MD −0.53 mmol/L, 95% CI −1.21 to 0.15 mmol/L; three randomized controlled trials, 324 participants), severe hypoglycaemic episodes (RD −0.01, 95% CI −0.04 to 0.02; seven randomized controlled trials, 553 participants), the rate of any hypoglycaemic episode (RD −0.75, 95% CI −2.21 to 0.72; five randomized controlled trials 232 participants) or difference in HbA1c (MD −0.19%, 95% CI −0.46% to 0.08%; five randomized controlled trials, 451 participants). A 2019 systematic review and meta-analysis of 22 randomized controlled trials (6235 participants) evaluated the effects of rapid-acting insulin analogues versus regular human insulin in children, adolescents and adults with type 1 diabetes (5). Primary outcomes were hypoglycaemia and postprandial glucose levels. HbA1c and quality of life were secondary outcomes. Rapid-acting insulin analogues were associated with lower postprandial glucose levels (MD −19.44 mg/dL, 95% CI −21.49 to −17.39; 15 randomized controlled trials, 5031 participants) compared with regular human insulin. For the outcome of HbA1c, pooled data from 15 randomized controlled trials (5204 participants) showed insulin aspart and insulin lispro to be associated with lower HbA1c levels compared with regular human insulin (MD −0.13%, 95% CI −0.16% to −0.10%). However, when assessed separately, only insulin aspart was associated with lower HbA1c compared with regular human insulin. Type 2 diabetes A 2018 Cochrane systematic review of 10 randomized controlled trials (2751 participants) assessed the effects of rapid-acting insulin analogues versus regular human insulin in non-pregnant adults with type 2 diabetes (6). For the primary outcome of all-cause mortality, mortality events were rare but occurred more frequently in the insulin analogue group (0.4% versus 0.2%, Peto odds ratio (OR) 1.66, 95% CI 0.47 to 6.64; three randomized controlled trials, 2519 participants; moderate-certainty evidence). No differences were observed between different types of

insulin analogues nor between treatment groups for severe hypoglycaemic events (outcomes not meta-analysed). For the secondary outcome of glycaemic control, no significant difference was seen between treatment groups in the change in HbA1c (MD −0.03%, 95% CI −0.16% to 0.09%); nine randomized controlled trials, 2608 participants; low-certainty evidence), with no differences observed between different types of insulin analogues. Pregnant women with pre-existing diabetes and gestational diabetes A 2017 Cochrane systematic review of five randomized controlled trials (554 women and babies) evaluated different insulin types and regimens in pregnant women with pre-existing type 1 or type 2 diabetes (7). Two of the included trials compared rapid-acting insulin analogues with regular human insulin, only one of which reported on outcome measures of interest of the review. For the main comparison of insulin lispro versus regular human insulin (one randomized controlled trial, 33 participants), there was very-low-quality evidence of no significant differences between treatment groups for perinatal death (relative effect not estimable), preeclampsia (risk ratio (RR) 0.68, 95% CI 0.35 to 1.30), caesarean section (RR 0.59, 95% CI 0.25 to 1.39) and birth trauma (relative effect not estimable). The 2018 systematic review that assessed efficacy and safety of rapid-acting insulin analogues in special populations with type 1 diabetes included two randomized controlled trials in people with pre-gestational type 1 diabetes and four randomized controlled trials in people with gestational diabetes (4). The results generally showed similar outcomes with rapid-acting insulin analogues and regular human insulin for glycaemic control, hypoglycaemic events and neonatal outcomes. In pregnant women with pre-existing type 1 diabetes, the largest trial randomized 322 women to receive insulin aspart or regular human insulin in combination with neutral protamine Hagedorn basal insulin and found that HbA1c levels were comparable between treatment arms at the end of the second and third trimesters. Postprandial plasma glucose increments, and mean plasma glucose levels at 90 minutes post-breakfast were significantly lower for insulin aspart. Insulin aspart was associated with a non-significant reduction in risk of major hypoglycaemic events (RR 0.72, 95% CI 0.36 to 1.46). Among trials in women with gestational diabetes, the results generally indicated insulin lispro to be at least as effective as or more effective than regular human insulin for glycaemic control.

Harms

Type 1 diabetes From the 2016 Cochrane systematic review in type 1 diabetes, for the outcome of severe hypoglycaemic episodes, rapid-acting insulin analogues were associated with a non-significant reduced risk of severe hypoglycaemia compared with human insulin (OR 0.89, 95% CI 0.71 to 1.12; seven randomized controlled trials, 2459 participants, very-low-quality evidence). For the outcome of weight gain, no significant difference was seen between treatment groups (MD −0.11 kg, 95% CI −0.25 kg to 0.04 kg; six randomized controlled trials, 2385 participants, moderate-quality evidence) (3). From the 2018 systematic review in special populations with type 1 diabetes, among children and adolescent trials, no significant difference was seen between rapid-acting insulin analogues and regular human insulin for severe hypoglycaemic events (risk difference (RD) 0.00, 95% CI −0.01 to 0.01; five randomized controlled trials, 1216 participants, low-quality evidence) (4). Among the trials on continuous subcutaneous insulin infusion, no significant differences were seen between treatment groups for severe hypoglycaemic episodes (RD −0.01, 95% CI −0.04 to 0.02; seven randomized controlled trials, 553 participants) or any hypoglycaemic episode (RD −0.75, 95% CI −2.21 to 0.72; five randomized controlled trials 232 participants). From the 2019 systematic review, results for all hypoglycaemic episodes per month showed no difference between rapid-acting insulin analogues and human insulin (risk rate (RR) 0.94, 95% CI 0.89 to 1.00; 22 randomized controlled trials, 6235 participants). However, in a sensitivity analysis excluding studies with a high risk of bias, rapid-acting insulin analogues were associated with fewer hypoglycaemic events per month compared with regular human insulin (RR 0.93, 95% CI 0.87 to 0.99; 20 randomized controlled trials, 6180 participants). Rapid-acting insulin analogues were associated with a reduced risk of nocturnal hypoglycaemia (RR 0.55, 95% CI 0.40 to 0.76; eight randomized controlled trials, 1995 participants) and severe hypoglycaemia (RR 0.68, 95% CI 0.60 to 0.77; 15 randomized controlled trials, 5945 participants) compared with regular human insulin (5). Type 2 diabetes From the 2016 Cochrane systematic review in type 2 diabetes, for the primary outcome of all-cause mortality, mortality events were rare but occurred more frequently in the insulin analogue group (0.4% versus 0.2%, Peto OR 1.66, 95% CI 0.47 to 6.64; three randomized controlled trials, 2519 participants; moderate-certainty evidence). No differences were observed between different types of insulin analogues nor between treatment groups for severe hypoglycaemic events (outcome not meta-analysed) (6).

Cost / cost effectiveness

The application identified and summarized the findings of 19 research articles considering cost, cost–effectiveness, budget impact and price of insulin (9–27). Most studies were conducted in high-income settings and published more than 5 years ago. In summary, the application highlighted that rapid-acting insulin analogues are more expensive than regular human insulin in various settings,

although production costs are relatively similar. The growing availability of biosimilars offers opportunities for price reductions. Despite higher upfront costs, insulin analogues may result in lower overall health-care costs due to a reduced incidence of hypoglycaemia, fewer hospitalizations and lower rates of diabetes-related complications. Cost–effectiveness studies in various settings suggest that rapid-acting insulin analogues can be cost-effective, especially for type 1 diabetes. For type 2 diabetes, the cost–effectiveness is more variable. Survey data from different countries show significant variation in the prices of rapid-acting insulin analogues. While insulin analogues are often more expensive than human insulin, increased availability of biosimilars and efforts in price negotiations may help to lower costs in the future.

WHO guidelines

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 include a strong recommendation (low-quality evidence) for the use of 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 (8). The recommendation was strong because evidence of better effectiveness of insulin analogues was lacking, and human insulin had a better resource-use profile. The guidelines also include a weak recommendation to 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 (moderate-quality evidence for severe hypoglycaemia) (8). WHO guidelines for the pharmacological management of gestational diabetes or pre-existing diabetes in pregnant women are not currently available.

Availability

Rapid-acting insulin analogues, including insulin lispro, insulin aspart and insulin glulisine, have wide global regulatory approval. Biosimilar versions of insulin aspart and/or insulin lispro are available in some settings.

Other considerations

The Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The technical department did not support the inclusion of rapid-acting insulin analogues on the Model Lists because of limitations in the evidence for benefits and the high costs of the medicines.

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