# Proposal for the addition of Rapid-Acting Insulin Analogues (Insulin lispro, Insulin aspart, and Insulin glulisine) to the WHO Model List of Essential Medicines for the treatment of adults with type 1 and type 2 diabetes mellitus and for gestational diabetes and to the Essential Medicines List for Children for the treatment of type 1 and type 2 diabetes

**Applicant:**
T1International

**Persons to contact:**

Christine Toavs, MSc
International Health Policy – London School of Economics and Political Science
T1International Global Advocacy Manager
Email: ctoavs@t1international.com

Luis Felipe Aceves Arias, MD, MSc
Health Policy, Planning and Financing – London School of Hygiene and Tropical Medicine/London School of Economics and Political Science
Certified Specialist in Internal Medicine
Email: luisfelipe.aceves@gmail.com

Elizabeth Pfiester, MSc
International Development and Humanitarian Emergencies – London School of Economics and Political Science
T1International Founder
Email: globaladvocacy@t1international.com

Marlene Chakhtoura, MD, MSc
Assistant Professor of Clinical Medicine
Calcium Metabolism and Osteoporosis Program
Director, Clinical Research Institute
Director, Research Personnel Program
Assistant Director, Scholars in HeAlth Research Program (SHARP) Summer
American University of Beirut-Medical Center
Email: mc39@aub.edu.lb

**Date of Submission:**
30 October 2024

# Section 1: Summary statement of the proposal for inclusion

We propose the addition of rapid-acting insulin analogues to the WHO Model List of Essential Medicines (EML) for type 1 and type 2 diabetes mellitus (T1DM and T2DM) and gestational diabetes. We specifically propose the addition of insulin lispro, insulin aspart, and insulin glulisine, including biosimilar products in vial and pen formulations. We propose that these should be added to the core EML for adults and EMLc for children.

As with long-acting insulin analogues, rapid-acting insulin analogues can enable more patients with diabetes to attain better glycaemic control, with more flexibility in administration timing and reduced severe hypoglycemic episodes for those living with diabetes mellitus.(1) The similarity in pharmacokinetic properties between rapid-acting insulin analogues and naturally-produced insulin presents a remarkable advantage of analogues over human insulins.(2) One of the key advantages of rapid-acting insulin analogues is their ability to support a basal-bolus regimen that closely mimics normal physiological insulin patterns, making it a fundamental approach for managing T1DM.(1)

With the addition of long-acting insulin analogue to the Essential Medicines List in 2021, it is time for rapid-acting insulin analogues to follow in order to further improve access and outcomes among people with diabetes mellitus. In patients with T1DM, it is highly unlikely that someone prescribed long-acting insulin analogue would not also be prescribed rapid-acting insulin analogue. The two are complimentary, as long-acting insulin analogues function as a background basal rate while rapid-acting insulin analogues is taken before meals or times of carb consumption and to quickly correct high or rising blood glucose levels.(3)

Including rapid-acting insulin analogues in the EML would garner more attention to insulin, list prices, and policies targeting high prices. Some countries have started to observe price reductions as a result of newly implemented policies, which has further widened disparities in diabetes care.(4–8) The EML listing may accelerate this promising pattern by facilitating dissemination of information on net prices and rebates across countries, identifying virtuous negotiations and limiting risk of price bubbles driven by opaque proposals made by companies.

The cost to produce analogue insulin is only slightly higher than production of human insulin.(9) Therefore the inclusion of rapid-acting insulin analogues will signal the vital importance of analogues in the List of Essential Medicines and, in turn, may catalyse the reduction of list prices. Currently, the insulin market does not hold the interest of patients reliant on insulin therapy and does not follow typical market patterns, as three companies control 96% of the insulin market by volume and 99% in terms of value globally.(10) The lack of robust competition leaves the world with a market insulated from price controls and inevitably strips patients of choice: choice of medicine, choice of cost, and choice of survival in many cases.(11)

Lastly, we believe patients should have the opportunity to choose between different types of insulin to use what works best for them. Survey data suggests that analogue insulins are preferred by most patients.(12,13)

## 1.1 Previous relevant submissions to the EML Expert Committee

Previous submissions have proposed the addition of long-acting insulin analogues to the WHO EML. The 2021 submission was accepted and long-acting insulin analogues were added into the 22nd WHO EML with the WHO Press Release noting:

> *"The move to list long-acting insulin analogues (insulin degludec, detemir and glargine) and their biosimilars, along with human insulin, is intended to increase access to diabetes treatment by expanding the choice of treatment…Long-acting insulin analogues offer some extra clinical benefits for patients through their prolonged duration of action, which ensures that blood glucose levels can be controlled over longer periods of time without needing a booster dose. They offer particular benefit for patients who experience dangerously low blood glucose levels with human insulin. The greater flexibility in timing and dosing of insulin analogues has been shown to improve quality of life for patients living with diabetes."(14)*

In the 2021 application to add (ultra-)long-acting insulin analogues to the WHO Model List of Essential Medicines, it was highlighted that the 2020 Lancet Commission report on diabetes argued:

> *"Insulin analogues are now widely used in many countries. Basal insulin analogues are better than human or animal insulins (eg, bovine and porcine sources) for minimising the risk of nocturnal hypoglycemia, and are particularly useful for basal–bolus regimens (ie, therapy involving multiple injections a day of long-acting or intermediate-acting insulin and short-acting or rapid-acting insulin at each meal). Nevertheless, human and biosimilar insulins are more affordable insulins in LMICs than insulin analogues. In patients with type 1 diabetes, basal–bolus insulin regimens offer better glycaemic control than twice daily regimens, if accompanied by the appropriate education of individuals with diabetes, family, and care providers with access to adequate supplies of needles, lancets, and testing strips for self-monitoring blood glucose concentration. However, the cost of self-monitoring is often higher than that of insulin. In some LMICs, the tariffs on insulin and self-monitoring supplies often reduce the affordability of these treatments.*
>
> *Many clinics still use insulin regimens twice a day, often with premixed insulin. These regimens are usually associated with higher HbA1c and more frequent hypoglycemia than are basal–bolus insulin regimens, especially when used with little or no self-monitoring of blood glucose concentration and diabetes education. However, other non-insulin determinants of quality of glycaemic control are also important. In LMIC settings, due to limited insulin, food insecurity, the unavailability of devices to self-monitor blood glucose and emergency glucagon injection kits, and scarce transport and emergency services, there is a tendency to reduce the dose of premixed insulins to avoid hypoglycemia. All of these factors can increase the risk of poor glycaemic control and complications that can adversely affect growth and quality of life. Even in HICs, poverty, varying health-care financing or insurance policies, lack of price transparency, complexity in supply chains, and insufficient competition among a few manufacturers have made insulin and supplies to self-monitor blood glucose concentration difficult to afford."(15)*

Health Policy Watch after (ultra-)long-acting insulin analogues were added to the WHO Model List of Essential Medicines reported:

> *"Scientific experts, civil society, and patient groups had met the proposal to include analogues in 2019 with stiff resistance, fearing that mainstreaming the newer drugs, which are more expensive, into the EML, could ultimately drive up prices for developing countries.*
>
> *But two years later, the use of analogues has expanded much more, while prices have decreased, with treatments no longer under patent protection in many countries. In settings where cost containment and efficient negotiations with insulin producers are in place, prices for insulin analogues are decreasing and aligning with those of human insulin."(16)*

## Section 2: Consultation with WHO technical departments

The relevant department is the WHO Department of Noncommunicable Diseases.

## Section 3. Name of organisation(s) consulted and/or supporting the application

*See letters of support in Annex 3.*

Nana Ama Barnes, MD
Executive Director, Diabetes Youth Care
*Partner organisation of T1International*
Internal Medicine Physician, Kaiser Permanente
Accra East, Ghana

Stéphane Besançon, MSc
Executive Director, Santé Diabète
*Partner organisation of T1International*
Associate Professor of Global Health, CNAM
Bamako, Mali

Katarina Braune, MD
Paediatrician, Diabetologist
*Global Advocate alumna of T1International*
Assistant Professor of Medical Informatics, Institute of Medical Informatics, Charité Universitätsmedizin Berlin, Germany

Justin Cirhuza Cikamola, MD, MMed, Phd
Doctor of Internal Medicine
Professor, Université Catholique de Bukavu
Bukavu, Democratic Republic of the Congo

Martha Gimono, MD
Consulting Physician, Sonia Nabeta Foundation
*Partner organisation of T1International*
St Mary's Hospital Lacor
Gulu, Uganda

Amit Gupta, MD, MBA, M.Phil., DTCD, MBBS
Joint Secretary, Diabetes india
Medical Director, Centre for Diabetes Care
Nagpur, India

Sroda Hottor, BSc BCHM, MBChB, MPH
Consulting Paediatrician, Sonia Nabeta Foundation
*Partner organisation of T1International*
Paediatrician, NF T1D Clinic at Sanford World Clinic Adenta
Accra, Ghana

Daniel Moore, MD, PhD
Director, Fellowship in Pediatric Endocrinology
Director, Pediatric Physician-Scientist Training Program
Faculty Leader, Edwards-Goodpasture MSTP College
Associate Professor of Pediatrics
Associate Professor of Pathology, Microbiology, and Immunology
Vanderbilt University Medical Center
Nashville, Tennessee, United States of America

Nkiruka Okoro, MD, MRes, MSc, BSc
Senior Clinical Assistant, Cardiology, Queen Elizabeth University Hospital
Glasgow, Scotland
Director, The Diabetic Concept
Abuja, Nigeria

Fabiola Prado, MD, PhD
Director, Department of Diabetes Education
Instituto Diabetcentro
*Partner organisation of T1International*
Guatemala City, Guatemala

Banshi Saboo, MD, PhD

Secretary, Diabetes India
Chairman and Chief Diabetologist - Diacare and Hormone Clinic
IDF Chair Elect South-east Asia
Global Council Member EASD
Ahmedabad, India

Veronica Sawicki, MBBS, DRCOG, DTMH
Executive Director, Help Madina
*Partner organisation of T1International*
Madina, Sierra Leone

Arianna Schouten, MSc
Senior Researcher, Knowledge Ecology International
*Collaborator organisation of T1International*
Amsterdam, Netherlands

Maham Tahir, MBBS
Medical Officer, Bahria International Hospital
*Co-Lead, Fight for Five Campaign, T1International*
Peer Leader, Meethi Zindagi
*Partner organisation of T1International*
Rawalpindi, Pakistan

## Section 4: Key information summary for the proposed medicine(s)

| | | | |
|---|---|---|---|
| International Nonproprietary Name (INN) | 1. Insulin lispro<br>2. Insulin aspart<br>3. Insulin glulisine | | |
| Anatomical Therapeutic Chemical (ATC) Code | 1. A10AB04<br>2. A10AB05<br>3. A10AB06 | | |
| ICD Classification | 5A10 type 1 diabetes mellitus<br>5A11 type 2 diabetes mellitus<br>5A14 diabetes mellitus, type unspecified<br>5A24 uncontrolled or unstable diabetes mellitus<br>5A13 diabetes mellitus, other specified type<br>JA63 diabetes mellitus in pregnancy | | |
| Indication | Treatment of patients with type 1 or type 2 diabetes mellitus who are at high risk of experiencing hypoglycemia with human insulin<br><br>Treatment of diabetes mellitus in pregnancy as diagnosed by the 2006 WHO criteria for diabetes | | |
| | | | |
| Dosage form | Strength | EML | EMLc |
| Injection | 100 IU/mL in 10 mL vial | Yes | Yes |
| | 100 IU/mL in 3 mL cartridge or pre-filled pen | Yes | Yes |

**Note on Language:**

Both rapid- and short-acting insulins are classified as bolus insulins and the terms “rapid” and “short” are sometimes used interchangeably in studies, usually denoted with the specific type (lispro, aspart, glulisine), and colloquial speech. This submission uses “rapid-acting” specifically for rapid-acting analogue insulins and “short-acting” specifically for regular human insulin, more broadly “analogue insulins” and “human insulins” respectively. Some references and letters of support use “short-acting insulin analogues ” to refer to rapid-acting insulin analogues including insulin lispro, insulin aspart, and insulin glulisine; they do not refer to human insulins.

## Section 5: Listing as an individual medicine or representative of a pharmacological class / therapeutic group

This proposal believes rapid-acting insulin analogues should be listed with a restricted square box, with insulin lispro representative of the class and insulin aspart and insulin glulisine included in the restricted square box. This proposal includes biosimilar insulins as evidence to date demonstrates safety and validates switching patients from originator to biosimilar insulin.(17) This proposal includes vials, pre-filled pens, and cartridges. Dose forms are the same for adults and for children

## Section 6: Information supporting the public health relevance

The T1D Index estimated global prevalence of T1DM at 8.4 million in 2021, with 1.5 million <20 years.(18) Prevalence also varied from 1.5 to 534 per 100,000, with T1DM accounting for <0.1 -- 17.8% of all diabetes in different countries. Despite the evidence for available effective treatment options, mostly represented by insulin, the quality of life of children and adolescents with T1DM remains poor, secondary to the need for frequent monitoring of glucose level, frequent administration of insulin, among others,(19) cardiovascular diseases represent the most common complication in T1DM, and one of the main causes of increased mortality.(20) An estimated 435,000 people <25 years received "minimal care".(18) Life expectancy varies across countries; while it reaches 61 years after 10 years of diagnosis of T1DM in HICs, Canada and USA, it is only 13 years in low income countries.(21) T1DM is associated with 0.1% of global Disability-adjusted life years (DALYs).(22)

People with other types of diabetes may also need rapid-acting insulin analogues. Diabetes affected an estimated 463 million people in 2019, or 9.3% of the global population, of which 79% live in low- and middle-income countries (LMICs).(23,24) It was responsible for over 1.5 million deaths and 2.79% of all global DALYs in 2019.(25) It is estimated that diabetes reduces life expectancy by 6 years when diagnosed at the age of 40.(19) Diabetes also significantly increases the risk of other NCDs including heart disease and cancer.

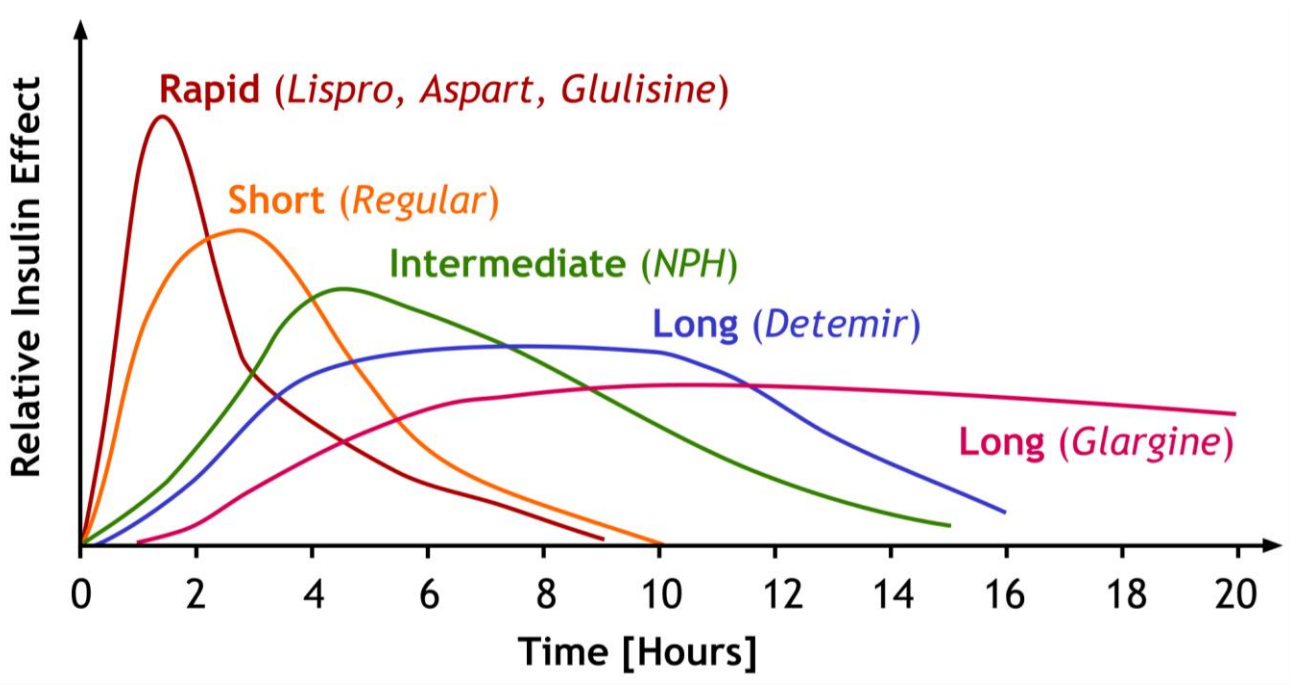
People diagnosed with T1DM require lifelong basal and prandial insulin injections. The amount of injections per day depends on the needs of the individual as diabetes manifests differently for everyone. Due to the chronic condition of T1DM and the constant balance between hyperglycemia and hypoglycemia, flexibility is a core tenet of insulin regimens. Flexibility to tailor insulin regimes greatly impacts treatment adherence and quality of life for both patients with T1DM and patients with T2DM requiring insulin therapy. Maintaining "glycemic control" within set glucose ranges leads to greater life expectancy and lower rates of complications.

Similarly, insulin pen formulations are preferred by 82% of people using insulins because it's easier to give the correct dose, less painful, and less stigmatising to use in public.(26) Insulin pens have been included in the EML for long-acting insulin and human insulin; additionally, reusable insulin pens could be more affordable than vial-and-syringe administration over the medium-to-long term.(27) Including insulin pens in the EML can reduce prices and put an end to the global double standard in diabetes care.

Thus flexibility to choose between available insulins can help mitigate negative factors affecting insulin therapy such as complicated dosing regimens, fear of hypoglycemic events, and injection site reactions.(28) This argument was put forth in the (ultra-)long-acting insulin analogue application to the WHO EML and applies to rapid-acting insulin analogues as well. While long acting insulin have been included in the WHO List of Essential Medicines, rapid acting insulin analogue vials and pens are not yet.(29)

The main advantages of insulin analogues over human insulin are rapid action profile, and therefore allowing flexibility in their administration, while reducing the risk of hypoglycemia.(30) Moreover, rapid-acting insulin analogues are only approved for use in designated insulin pumps.(4,23)

***Figure 1. Comparison of time-action profiles for different insulin types***




Adapted from M.Komorniczak CC-BY licence.(25)

## *Table 1. Comparison of peak action and duration of action for rapid-acting insulin analogues and human insulin*

| Type | Onset (min) | Peak Action (hr) | Duration of Action (hr) |
|---|---|---|---|
| Rapid-acting | | | |
| Insulin lispro | <15 | 1-2 | 4-6 |
| Insulin aspart | <15 | 1-2 | 4-6 |
| Insulin glulisine | <15 | 1-2 | 4-6 |
| Short-acting or regular | | | |
| Human insulin | 30-60 | 2-4 | 6-8 |

Adapted from Hirsch et al under CC-BY licence.(24) *100 units per mL.

The faster onset time leads to maximal reduction of postprandial glucose excursions compared to human insulin.(31,32) Further, higher peak concentrations of rapid-acting insulin analogues combined with this shorter interval for pre-meal insulin injection is more convenient for patients and leads to increased adherence to prescribed injection timing guidelines.(33)

Absorption is a key factor for insulin administration and effectiveness. Subcutaneous insulin absorption varies about 15% within an individual and 30% between patients.(34) Various injection sites include abdomen, deltoid, gluteus, and thigh. Blood flow differences between these injection sites significantly impacts rate of absorption. Human insulin absorbs 2 times faster when injected into the abdomen versus the thigh.(35) This wide variance requires patients to avoid randomly using different body regions for injections and maintain an injection site pattern. Conversely, insulin aspart, glulisine and lispro show less day-to-day variation in absorption rates and less absorption variation from the different body regions allowing patients more freedom and certainty over their injection sites than regular human insulin.(36–39)

Additionally, pre- and post-meal injections are approved for insulin lispro. This allowance is particularly useful for young children with T1DM and ill, insulin requiring hospitalised patients as the amount of carbohydrates consumed per meal can be unpredictable.(23) There are no significant differences in post meal glucose levels, rates of hypoglycemia, or HbA1c between pre- and post-meal injections in prepubertal children.(40)

Glucagon is the key treatment for insulin-induced hypoglycemia for patients who either cannot ingest oral glucose or cannot obtain IV access to prevent irreversible brain damage. Glucagon is listed in the WHO EML however, glucagon availability varies between countries and is often low in supply and costly in low-resource settings.(41)

# Section 7: Treatment details

Insulin is the mainstay of insulin-dependent diabetes mellitus treatment. Human insulin has been available on the WHO EML since the first one in 1977. Long-acting insulin analog has been available on the WHO EML since 2021. Rapid-acting insulin is given to cover the carbohydrate content of the meals, and/or to correct for hyperglycemia, or as a continuous infusion in insulin pumps. The total daily dose of rapid-acting insulin varies. The dose depends on several factors including carbohydrates intake, level of physical activity, medications, renal function, insulin resistance, stress and illness. The benefit of rapid-acting insulin analogue is that it can be given as needed to counteract high blood glucose levels or carbohydrates ingested at mealtimes.

The injection should be given within 15 minutes before a meal or immediately after a meal.

The main adverse events associated with insulin are hypoglycemia, lipodystrophy, weight gain and peripheral edema. The risks associated with rapid- acting insulin can be prevented by appropriate matching of insulin dose to glucose level and carbohydrate intake, rotating the insulin injection site, and by monitoring salt and caloric intake.

## 7.1 Patient eligibility criteria

There is insufficient clinical information on the use of insulin lispro in children with type 2 diabetes or in children with type 1 diabetes under three years of age.(36,42) There is insufficient clinical information on the use of insulin aspart in children with type 2 diabetes or in children with type 1 diabetes under two years of age.(37,43) There is insufficient clinical information on the use of glulisine in children with type 2 diabetes or in children with type 1 diabetes under six years of age.(38,44)

## 7.2 Diagnostic and/or monitoring test requirements

Diagnostic tests for diabetes mellitus include key assessments such as haemoglobin A1c (HbA1c) which reflects average blood glucose over a 2-3 month period; in addition, blood sugar test, fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), and random plasma glucose can be used. Results of higher ranges for all tests typically indicate diabetes or prediabetes (in T2DM).

Monitoring tests also include a routine HbA1c usually performed every three to six months and daily or continuous glucose blood tests (depending on severity and type). These tests are further described in section 7.5. Additional monitoring assessments include urine ketone testing, blood pressure and lipid profile monitoring to manage cardiovascular risk, eye and foot exams, and kidney function tests.

## 7.3 Treatment Administration Requirements

### 7.3.1 Administration and storage

Administration methods of rapid-acting insulin analogues include subcutaneous injections via syringes, insulin pens (prefilled or refillable), and needle-free injectors (less common). Insulin can also be delivered through subcutaneous infusion via insulin pumps which provide Continuous Subcutaneous Insulin Infusion (CSII). Insulin can also be administered intravenously.(45)

Compounding is not required for rapid-acting insulin analogues as they are commercially available in ready-to-use formats.

Insulin should be optimally stored at refrigerated temperatures (2-8 degrees centigrade) and must never be allowed to freeze. Extreme temperatures or excess agitation should be avoided during storage to prevent loss of potency of the formulation. When a formulation is in use, insulin should be kept unrefrigerated to minimise local injection site irritation and should be kept away from excess heat or sunlight. Insulin exposed to temperatures higher than 37 degrees centigrade should be discarded.

### 7.3.2 Healthcare setting

A number of healthcare settings are required for the ongoing treatment of diabetes mellitus. Ambulatory care is the most common setting for diagnosis while specialised treatment facilities such as endocrinology clinics and diabetes centres oversee initiation and monitoring of rapid-acting insulin therapy. After initial education and training, most patients can independently manage their insulin therapy. Endocrinologists, diabetes educators, and nurses are the providers generally involved in a patient's insulin therapy management.(46) Hospital and inpatient settings are also a frequent place for diagnosis and are required for emergency cases including diabetic ketoacidosis (DKA), severe hypoglycemia, and other diabetes related complications.

## 7.4 Required skill levels of healthcare providers and their availability.

Multiple healthcare providers aid in treatment management including endocrinologists, certified diabetes educators (CDEs), primary care physicians, nurse practitioners, pharmacists, and home nurses and caregivers.

The required skills levels for each healthcare provider are identical to those needed for human and long-acting insulin analogues. Dose regimens depend upon the patient and insulin administering device. Availability of providers differs between countries, especially High Income Countries (HIC) versus LMICs and rural versus urban settings. Though this variance in availability is the same, regardless of the type of insulin prescribed or in use.

## 7.5 In vitro diagnostics tests

Two companion in vitro diagnostics tests are required for appropriate use of rapid-acting insulin analogues as well as initial diagnosis which also informs the proceeding treatment plan. The two tests are listed on the WHO Model List of Essential In Vitro Diagnostics as Glucose and Haemoglobin A1c (HbA1c).(47) The following table illustrates the setting/facility level, purpose type, purpose, and code of

the diagnostic tests associated with each overarching category. Continuous glucose monitors (CGMs) are another diagnostic test under the Glucose category that measures glucose in interstitial fluid that are not currently listed on the WHO Model List of Essential In Vitro Diagnostics.

### *Table 2. Diabetes Mellitus companion diagnostic tests according to the WHO Model List of Essential In Vitro Diagnostics 2024*

| Glucose<br>Diabetes Mellitus | | | | | |
|---|---|---|---|---|---|
| Diagnostic Test | Setting/facility level | Purpose type | Purpose | ICD11 Code | WHO Supporting document(s) link(s) |
| Dipstick | 1. No Laboratory | Aid to diagnosis, Screening | To aid in the diagnosis of diabetes mellitus (if blood glucose testing is not available); To screen for T2DM | 5A14 | HEARTS-D: diagnosis and management of T2DM (2020) https://www.who.int/publications/i/item/who-ucn-ncd-20.1; https://www.who.int/health-topics/diabetes#tab=tab_1 |
| Glucose meter | 1. No Laboratory | Diagnosis, Monitoring, Screening | To diagnose and monitor T1DM and T2DM; To diagnose impaired fasting glucose/impaired glucose tolerance; To screen for T2DM diabetes mellitus and impaired fasting glucose/impaired glucose tolerance | 5A14 | HEARTS-D: diagnosis and management of T2DM (2020) https://www.who.int/publications/i/item/who-ucn-ncd-20.1; https://www.who.int/health-topics/diabetes#tab=tab_1 |
| Optical methods, automated chemistry analyser if available | 2. Laboratory | Diagnosis, Monitoring, Screening | To diagnose and monitor T1DM and T2DM; To diagnose impaired fasting glucose/impaired glucose tolerance; To screen for T2DM and impaired fasting | 5A14 | HEARTS-D: diagnosis and management of T2DM(2020) https://www.who.int/publications/i/item/who-ucn-ncd-20.1 |

| | | | | | |
|---|---|---|---|---|---|
| | | | glucose/impaired glucose tolerance; Note: When used for emergency or critical care, results are time-sensitive. | | |
| Haemoglobin A1c (HbA1c)<br>Diabetes Mellitus | | | | | |
| Diagnostic Test | Setting/facility level | Purpose type | Purpose | ICD11 Code | WHO Supporting document(s) link(s) |
| Handheld and small analysers | 1. No Laboratory | Diagnosis, Monitoring | To diagnose and monitor diabetes mellitus | 5A14 | HEARTS-D: diagnosis and management of T2DM(2020) https://www.who.int/publications/i/item/who-ucn-ncd-20.1; https://www.who.int/health-topics/diabetes#tab=tab_1 |
| Immunoassay | 2. Laboratory | Diagnosis, Monitoring | To diagnose and monitor diabetes mellitus | 5A14 | HEARTS-D: diagnosis and management of T2DM(2020) https://www.who.int/publications/i/item/who-ucn-ncd-20.1 |

# Section 8: Review of evidence for benefits and harms

Two key outcomes–rate of hypoglycemic events and HbA1c–can be considered measures of clinical effectiveness or measures of (reduced) harm. This section presents evidence for both harms and effectiveness (benefits) for rapid-acting insulin analogues. Advantages associated with flexibility in dosing regimes, as described above, are not included in this section due to the lack of corresponding hard endpoint measured in empirical studies.

## 8.1 Summary of evidence of comparative effectiveness

This review uniquely integrates multiple systematic reviews and meta-analyses, offering a comprehensive perspective on the consistency of key findings and their clinical implications. The quality of this evidence remains mostly low due to various limitations, including potential biases and inconsistencies in reporting outcomes across studies.

The systematic reviews cited in this section are of high quality and adhered to predefined methodologies. Differences in conclusions among these reviews likely arise from variations in study inclusion criteria and statistical methodologies employed. Moreover, the clinical significance of differences between rapid-acting insulin analogues and human insulin has been interpreted differently by various independent review teams.

A notable strength of this evidence review is its focus on direct head-to-head comparisons, contrasting rapid-acting insulin analogues with human insulin, a comparator with well-established efficacy. This approach enhances the reliability of the findings and provides a clearer understanding of the comparative effectiveness of insulin therapies in managing diabetes. A limitation of this literature review is that data mostly comes from high income countries and in highly controlled settings. This could lead to outcomes with less incidence of hypoglycemia than field research in LMIC.

## 8.2 Search strategy and identified studies

We defined our PICO question as follows:

- Population: Children and adults with insulin dependent diabetes (T1DM, and other non-auto-immune insulin dependent DM)
- Intervention: insulin analogues (fast/rapid acting insulin)
- Comparator: regular human insulin
- Outcomes: benefits, harm/adverse events, cost and cost effectiveness
- Benefits include all-cause mortality, microvascular complications (retinopathy, neuropathy, nephropathy), macrovascular (cardiovascular disease, cerebrovascular disease, peripheral vascular disease), glycemic control (measured by glycosylated haemoglobin A1c (HbA1c), fasting glucose), health related quality of life
- Harms include hypoglycemia, severe hypoglycemic events, adverse events

**Search strategy:**

We searched for systematic reviews/meta-analysis (SR/MA) on the topic in PubMed, Medline and Embase using MESH terms relevant to diabetes mellitus, regular human insulin, insulin analogues, and by limiting to SR/MA; the search period was 2015-2024.

Search on PubMed was as follows:

((("Diabetes Mellitus"[Mesh]) AND (("Insulin Aspart"[Mesh] OR "Insulin, Short-Acting"[Mesh] OR "Insulin Lispro"[Mesh]) OR ("Insulin Aspart"[Mesh] OR "Insulin, Short-Acting"[Mesh] OR "Insulin Lispro"[Mesh]))) ) AND ("insulin, regular, human"[MeSH Terms] OR ("insulin"[All Fields] AND "regular"[All Fields] AND "human"[All Fields]) OR "human regular insulin"[All Fields] OR "insulin regular human"[All Fields] OR ("isophane insulin, human"[MeSH Terms] OR ("isophane"[All Fields] AND "insulin"[All Fields] AND "human"[All Fields]) OR "human isophane insulin"[All Fields] OR "isophane insulin human"[All Fields])

OR ("insulin, regular, pork"[MeSH Terms] OR ("insulin"[All Fields] AND "regular"[All Fields] AND "pork"[All Fields]) OR "pork regular insulin"[All Fields] OR "insulin regular pork"[All Fields]))

The search strategy was reproduced in Medline and Embase.

We identified six systematic reviews and meta-analyses that addressed our question: one in adults T1DM (Fullerton 2019), one in T2DM (Fullerton 2018), one in children and adolescents with T1DM (Norgaard 2018), two in pregnant persons with pre-existing diabetes (O'Neil 2017, De Jong 2016), and one in pregnant persons with gestational diabetes mellitus (GDM) (Norgaard 2018). One additional systematic review (Melo 2019), which fit inclusion criteria but was not returned by the database search, was added after expert recommendation.

Meta-analyses of double-blind RCTs have found convincing evidence for analogues offering reduced hypoglycaemic events only in children and adolescents. However, the number of double-blind RCTs comparing rapid-acting analogues to RHI is limited, due to analogues being, by now, well-established. A meta-analysis that included open-label trials (Melo 2019), found that rapid-acting analogues led to reduced rates of hypoglycemia with a convincing effect size, and across a range of different types of hypoglycaemia.

We followed the GRADE methodology for evaluating the level of evidence, as reported in the systematic reviews or completed the evaluation ourselves in case the level of evidence was not reported.(48)

## 8.3 Summary of available data

### 8.3.1 Type 1 diabetes

#### Adults

*Fullerton et al 2019*

We identified a Cochrane systematic review comparing rapid-acting insulin analogues to human insulin, in adults with T1DM, updated in 2019 (Fullerton 2019). The systematic review aimed to assess all-cause mortality, micro and macrovascular complications, health related quality of life, in addition to Hba1c as a marker of efficacy, and adverse events including hypoglycemia.(49)

The search for this review was conducted in the following databases: Medline, Embase, the Cochrane library and trials registry, until 2015. The SR included 9 trials with a total number of 2693 participants. Six out of nine studies assessed insulin lispro and three out of nine used aspart and no trials on glulisine.

#### Efficacy data

The systematic review did not identify any data on mortality, vascular complications or quality of life.(49) There was a low level of evidence for a significant difference in Hba1c of 0.15% (-0.1%; -0.2%),

favouring insulin analogues; the level of evidence was downgraded secondary to inconsistency in reporting the results and indirectness The effect did not depend on the type of insulin used, Aspart or Lispro.(49)

### Safety data

The SR evaluated the risk of hypoglycemia, severe nocturnal hypoglycemia and weight, known adverse effects of insulin.

The risk of hypoglycemia did not differ between human insulin and insulin analogues. However, one main challenge was that the assessment of this parameter was not blinded, implying a high risk of bias. The risk of severe hypoglycemic episodes also did not differ between groups. However, we are very uncertain about the estimate. The quality of the evidence was considered very low, due to a high risk for performance bias, pooling of different outcome definitions and participant populations and wide confidence intervals being compatible with both beneficial and harmful.

There was no difference in weight between human insulin and insulin analogues, MD -0.11(-0.25; 0.04), based on a moderate quality of the evidence. Other adverse events also did not differ between insulin groups

### *Table 3. Summary of findings (SOF) table reproduced from Fellerton 2019(49)*

| Outcome | human insulin | Rapid-acting insulin analogues | Relative effect (95% CI) | Number of participants (studies) | Quality of evidence (GRADE)[2] with rational |
|---|---|---|---|---|---|
| All-cause mortality | One death in 6 trials reported as adverse event | | - | - | - |
| Microvascular complications | Not reported | | - | - | - |
| Macrovascular complications | Not reported | | - | | - |
| Severe hypoglycemia | 166 per 1000 | 150 per 1000 | OR 0.89 (0.71 to 1.12) | 2459 (7) | Very low (performance bias, heterogeneity, imprecision) |
| Health-related quality of life | "Health-related quality of life was either only assessed in subpopulations of 3 trials or insufficiently reported. Over all, there was no clear evidence for a substantial effect of short-acting insulin analogues on this outcome" [1] | | | | |
| HbA1c (%) at follow up | Mean 6.3-9.3% | Mean was 0.15% lower | - | 2608 (9) | Low (inconsistency, indirectness) |

| | | | | | |
|---|---|---|---|---|---|
| | | (0.2 lower to 0.1 lower) | | | |

[1] Taken verbatim from Fellerton 2019 "Health-related quality of life was either only assessed in subpopulations of 3 trials or insufficiently reported. Over all, there was no clear evidence for a substantial effect of short-acting insulin analogues on this outcome"
[2] Grading of the evidence as reported in paper

Noteworthy, this Cochrane review conducted a rigorous study quality assessment, and it gives a conservative interpretation of the differences between insulin analogues and human insulin.

### Children and adolescents with type 1 diabetes mellitus

*Norgaard et al 2018*

We identified one SR/MA comparing rapid-acting insulin analogues to human insulin in children with T1DM.(50) The review searched 3 databases without any time limit, until 2017. It identified 5 studies in children and adolescents, and 6 studies in patients on continuous subcutaneous insulin infusion (CSII).(50) The outcomes of interest were related to glycemic control including HbA1c, fasting glucose, postprandial glucose, hypoglycemia, the occurrence of diabetic keto-acidosis.

Based on the 5 studies in children and adolescents, there was no difference in the rate of severe hypoglycemia between human insulin and insulin analogues; the quality of the evidence was downgraded, due the study design being open label.

The evidence in patients on CSII is based on 6 studies, the majority being open-label. There was no difference in fasting glucose level, but a significantly lower postprandial glucose, favouring insulin analogues, based on 3 studies, 324 participants, with low heterogeneity (MD -1.63(-1.71;-1.54), $I^2$ 0%). Similarly, HbA1c was significantly lower in patients on insulin analogues, compared to human insulin, based on 5 studies, 451 participants, with a high heterogeneity [MD -0.19(-0.46; -0.08), $I^2$ 90%). There was no significant difference in the risk of hypoglycemia.

## *Table 4. Summary of findings (SOF) table based on data presented in Norgaard 2018(50)*

| Outcome | human insulin | Rapid-acting insulin analogues | Relative effect (95% CI) | Number of participants (studies) | Quality of evidence (GRADE)[1] with rational |
|---|---|---|---|---|---|
| Children and adolescents | | | | | |
| Severe hypoglycemia (N) | 14/623 | 14/593 | Risk difference -0.00 (-0.01; 0.01) | 1216 (5) | Low (open label trials, imprecision) |
| Users of continuous subcutaneous insulin infusion (CSII) | | | | | |
| Fasting glucose (mmol/L) | 6.5-7.7 | Mean difference 0.53 lower (1.21 lower to 0.15 higher) | Mean difference -0.53(-1.21; 0.15) | 324 (3) | Low (open label trials, high heterogeneity) |
| Postprandial glucose (mmol/L) | 6.8-9.4 | Mean difference 1.63 lower (1.71 lower to 1.54 lower) | - | 460(5) | Moderate (open label trials) |
| Severe hypoglycemia (N) | 8/251 | 10/282 | Risk difference -0.01(-0.04;0.02) | 533(7) | Very low (open label trials, high heterogeneity and imprecision) |
| Any hypoglycemia (N per patient per month) | 4-11 | Mean difference 0.75 lower (2.21 lower to 0.72 lower) | - | 232 (5) | Low (open label trials, high heterogeneity) |
| Change in HbA1c (%) | (-0.62) to 0.18 | Mean difference 0.19 lower (0.46 lower to 0.08 lower) | - | 451(5) | Low (open label trials, high heterogeneity) |

[1] Grading of the evidence not reported in paper but done by one of the authors of this document using the risk of bias assessment provided in the paper supplementary material

[2] The risk of any hypoglycemia was also not significantly different between insulin analogues and human insulin

### Additional data

*Melo et al 2019*

One systematic review and meta-analysis by Melo et al evaluated the impact of insulin analogues compared to human insulin on postprandial glucose, HbA1c level and the risk of hypoglycemia in children and adults with T1DM.(1) It included trials of at least 4 weeks' duration, published until 2017.

### Efficacy data

Post-prandial glucose was lower with insulin analogues compared to human insulin, based on 15 trials, 5031 participants, with high heterogeneity [MD -19.4 mg/dl (-21.5; -17.4), $I^2$ 69%]. Similarly, results on HbA1c favoured insulin analogues compared to human insulin, based on 9 studies, 5204 participants, with a high heterogeneity [MD -0.13% (-0.16; -0.1), $I^2$ 73%] (Melo 2019).

Melo et al identified five studies that assessed quality of life and patient satisfaction. Two of them showed significant results favouring insulin analogues, while three studies did not show any difference between human insulin and analogues.(1)

### Safety data

There was no difference in the risk of any hypoglycemia between insulin analogues and regular human insulin, based on 22 studies, 6235 participants [RR 0.94(0.89;1.00)]. However, in a sensitivity analysis excluding studies with a high risk of bias, there was a significant reduction in the risk of hypoglycemia with insulin analogues by 7%, compared to human insulin, based on 20 studies, 6180 participants [RR 0.93 (0.87; 0.99) with a high heterogeneity, $I^2$ 83%]. The risk of nocturnal hypoglycemia was significantly reduced by 45% with insulin analogues compared to human insulin, based on 9 trials, 1995 participants, with a wide confidence interval and high heterogeneity [RR 0.55 (0.40; 0.76) with a high heterogeneity, $I^2$ 84%]. The risk of severe hypoglycemia was reduced by 32% based on 15 trials, 5945 participants [RR 0.68(0.60; 0.77, with low heterogeneity $I^2$ 0%].(1)

Noteworthy that this review had several limitations. It did not have a pre-registered protocol, and the meta-analysis combined data from children, adolescents and adults.(1)

## 8.3.2 Type 2 diabetes mellitus

*Fullerton et al 2018*

We identified one Cochrane SR/MA comparing rapid-acting insulin analogues to human insulin for adults, non-pregnant, with T2DM.(51) The review searched Medline, Embase, Cochrane and registries, including clinicaltrials.gov and WHO ICTRP.(51) The SR identified 10 trials, with a total number of 2751 participants; 1388 received insulin analogues and 1363 received human insulin. The outcomes of interest were all-cause mortality, micro and macro-vascular diseases, Hba1c changes and non-severe hypoglycemia.

### Efficacy data

There was no significant difference in all-cause mortality OR 1.66(0.47; 6.64), moderate certainty evidence; there was no difference between insulin types. None of the studies reported on micro or macro-vascular diseases.

### Safety data

Six trials reported on the rate of severe hypoglycemia. The incidence of such events was very low, and therefore, there was no difference in the rate of hypoglycemia between insulin analogues and human insulin. Similarly, there was no significant difference in the achieved HbA1c between the treatment arms, and there was no difference between insulin types.

## *Table 5. Summary of findings (SOF) table reproduced from Fullerton 2018(51)*

| Outcome | Risk with human insulin | Risk with rapid-acting insulin analogues | Relative effect (95% CI) | Number of participants (studies) | Quality of evidence (GRADE) |
|---|---|---|---|---|---|
| All-cause mortality | 2 per 1000 | 4 per 1000 | Odds Ratio 1.66 (0.41; 6.64) | 2519(6) | Moderate (imprecision) |
| Microvascular complications | Not reported | | - | - | - |
| Macrovascular complications | Not reported | | - | - | - |
| Severe hypoglycemia (N) | Results are diverse and small number of events; effect uncertain | | | 2509(6) | Low (high risk of performance and detection bias) |
| Non-severe hypoglycemia (N per participant per month) | 0.6-2.5 | Mean difference 0.08 events per participant per months higher (0.00 lower to 0.16 higher) | - | 2667(7) | Very low (high risk of bias, inconsistency, indirectness) |
| Health-related quality of life | "Health-related quality of life was either assessed in subpopulations of 2 trials, or insufficiently reported. The effects of short-acting insulin analogues compared with regular human insulin for this outcome are uncertain"[1] | | | | |
| HbA1c (%) at follow up | Mean change -0.1 to 2.3% | Mean difference 0.3% lower (0.16 lower to 0.09 higher) | | 2608 (9) | Low (inconsistency and imprecision) |

[1] Taken verbatim from Fullerton 2018

### 8.3.3 Pregnant persons with pre-existing diabetes

*O'Neil et al 2017*

We identified a Cochrane SR/MA on insulin use in pregnant persons with pre-existing diabetes, T1DM or T2DM.(52) The SR searched the Cochrane Pregnancy and Childbirth Group's Trials Register, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform, in addition to screening of citations described in the included studies.(52) The review identified only two trials comparing human insulin to rapid-acting insulin analogues, and one of them only included the outcomes of interest.(53) There was no difference in perinatal death, preeclampsia, caesarean section and birth trauma, between treatment arms, based on very low evidence, downgraded secondary to high risk of bias, small sample size (with small number of events) and a very wide confidence interval.(52) Similarly, there was no difference in the number of hypoglycemia and hyperglycemia episodes requiring intervention, nor postprandial glucose levels at different timepoints.(52)

## *Table 6. Summary of findings (SOF) table reproduced from Oneil 2017(52)*

| Outcome | Risk with human insulin | Risk with rapid acting insulin analogues (lispro) | Relative effect (95% CI) | Number of participants (studies) | Quality of evidence (GRADE) |
|---|---|---|---|---|---|
| Macrosomia (N) | Not reported | | - | - | - |
| Perinatal death (N) | 0 per 1000 | 0 per 1000 | Not estimable | 33 (1) | Very low (high risk of bias and other biases) |
| Pre-eclampsia (N) | 647 per 1000 | 440 per 1000 | Relative risk 0.68 (0.35 to 1.3) | 33 (1) | Very low (high risk of bias, one study with design limitations, small sample size with few events, wide confidence interval) |
| Caesarean section (N) | 529 per 1000 | 312 per 1000 | Relative risk 0.59 (0.25 to 1.39) | 33 (1) | Very low (high risk of bias, one study with design limitations, small sample size with few events, wide confidence interval) |
| Foetal anomaly (N) | 59 per 1000 | 21 per 1000 | Relative risk 0.35 (0.02 to 8.08) | 33 (1) | Very low (high risk of bias, one study with design limitations, small sample size with few events, wide confidence interval) |
| Birth trauma (N) | 0 per 1000 | 0 per 1000 | Not estimable | 33 (1) | Very low (high risk of bias, one study with design limitations, small sample size with no events) |

*Norgaard et al 2018*

We identified another SR by Norgaard et al (see description above) that identified 2 trials in pregnant persons with pre-existing T1DM. One of them was included in O'Neil and described above.(53) The other trial enrolled persons who were either pregnant or planning to become pregnant (got pregnant during the follow up), and the outcomes of interest were reported for both groups together.(54) There was no difference in glucose measurements at different time points nor HbA1c level. There was a trend for a lower rate of hypoglycemic events, favouring insulin analogue, compared to human insulin; However, the results did not reach statistical significance.(54)

### 8.3.4 Pregnant persons with gestational diabetes mellitus (GDM)

#### Efficacy data

One systematic review identified 4 trials with persons with GDM, comparing rapid-acting insulin analogues with human insulin.(50) Two studies reported on postprandial glucose and showed lower values with insulin analogues compared to human insulin; one of them assessed 1-h postprandial glucose level, evaluated after a standardised breakfast at 27 weeks, the other assessed postprandial glucose at 6 weeks. The data is limited by the low certainty evidence (limited description of allocation concealment, open label design).(50)

#### Safety data

The reporting on hypoglycemia was scarce. One study did not report on this outcome, another study had no hypoglycemic events, and a third study showed a similar rate of symptomatic hypoglycemia and a lower number of minor hypoglycemia, favouring insulin analogues. The evidence was of very low certainty, secondary to high risk of bias (limited description of allocation concealment, open label design), and low number of events for hypoglycemia.(50)

## Section 9: Summary of recommendations in current clinical guidelines

The last updated WHO guidelines for diabetes mellitus was released in 2018. The 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 mellitus" currently only address the use of human insulin. Analogue recommendations are not yet included.(55)

Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy is outlined in the WHO guideline.(56) There are some differences in the approach to management of women with diabetes in pregnancy compared to gestational diabetes. Patients with gestational diabetes mainly use antidiabetic oral medications however, few need insulin to reach their blood glucose goals. The difference in treatment and management are outlined in existing evidence-based guidelines.(57)

Recommendations from other scientific societies:

The American Diabetes Association (ADA) in the latest guidelines in 2024, stated “For most adults with type 1 diabetes, insulin analogues (or inhaled insulin) are preferred over injectable human insulins to minimise hypoglycemia risk” Level of evidence A, Clear evidence from well-conducted, generalizable randomised controlled trials that are adequately powered, using the American Diabetes Association (ADA) evidence-grading system for “Standards of Medical Care in Diabetes”(58)

The NICE/ISPAD guidelines state the current preferred method is the basal bolus method, with intermediate or long-acting insulin given once or twice a day, and short acting insulin given three to five times a day before meals, adjusted according to the amount of food to be eaten.(59)

# Section 10: Summary of available data on comparative cost and cost-effectiveness

## 10.1 Search Strategy

We conducted a systematic literature review to identify research estimating the cost of treatment, cost-effectiveness, budget impact, and price of insulin analogues in different settings. All original research articles could be included, with no restrictions of language or search period.

The original search strategy was developed on OVID Embase as follows:

| # | Query |
|---|---|
| 1 | (insulin aspart or insulin lispro or insulin glulisine).af. |
| 2 | (insulin and rapid and analog*).af. |
| 3 | 1 OR 2 |
| 4 | (insulin AND regular and human).af. |
| 5 | (insulin AND isophane AND human).af. |
| 6 | (insulin AND regular AND pork).af. |
| 7 | 4 OR 5 OR 6 |
| 8 | 3 AND 7 |
| 9 | (cost OR price OR budget).af. |
| 10 | 8 AND 9 |

This strategy was reproduced in PubMed, Medline, and Cochrane databases.

After resolving duplicates, 512 articles were screened by two authors (CT and LFAA) for inclusion. Both authors solved conflicts through open debate when needed. The review process identified 19 relevant articles. A PRISMA flow diagram can be found in Annex 1.

The quality of evidence was rated according to the GRADE system and supported by the Critical Appraisal Skills Programme (CASP) tool. A table with detailed information about the quality rating of included articles is presented in Annex 2.

## 10.2 Summary of available data

The studies included a wide range of patients, which might increase the confidence in the findings. Patients with T1DM and T2DM were represented comparably in the studies. Pregnant persons with diabetes were also included in some studies. Although most of the costing and cost-effectiveness studies were developed in high-income settings, some of them were conducted in middle-income countries.

The studies reported that the price of rapid-acting insulin analogues were higher than the price of human insulin in a wide range of settings, though cost of production cost differences are minimal. As rapid-acting insulin analogues use increases, this encourages information-sharing on prices, especially net prices, between countries. Increased use boosts competition and draws more focus to their pricing and the policies designed to control or reduce high costs. Price reduction trends have already begun and EML inclusion might accelerate this pattern.

In the long term, the total costs of diabetes treatment becomes similar or even lower with the use of insulin analogues. This is related to a lower rate of complications, which leads to a reduced demand for high-cost treatments and health care services. In addition, pricing studies show a window of opportunity to decrease procurement prices of insulin analogues, especially with the increase in availability of biosimilars. These arguments should encourage policymakers to consider the inclusion of insulin analogues into the health system's medicine purchase list as a strategy to minimise costs in the long term.

### 10.2.1. Cost of treatment with rapid-acting insulin analogues

Two studies determined medical costs associated with treatment with human insulin and rapid-acting insulin analogues.

Both studies were conducted in the United States setting. Both studies used quasi-experimental methods (i. e., propensity score matching) to reduce the risk of selection bias. Neither study made a distinction between patients with T1DM and T2DM, and therefore the results are reported for diabetes in general. One study specifically excluded patients with GDM. Overall, the quality of evidence was moderate.

*Hall et al. 2003*

Through a retrospective analysis, the authors compared cost and utilisation between insulin lispro users and human insulin users. Data from 14 United Healthcare affiliated health plans were used to identify patients who continuously enrolled with claims for either insulin lispro or human insulin between 1998 and 1999. A propensity score-matching approach was employed to control for baseline difference between the two groups such as age, gender, comorbidities, and oral hypoglycemic use.

The authors found that insulin lispro users had more office visits and pharmacy prescriptions but fewer inpatient hospitalizations compared to human insulin users. The low inpatient hospital costs offset the significantly higher pharmacy and office visit costs. Total healthcare costs were not significantly different between the two groups. However, insulin lispro users experienced fewer hospitalizations for hypoglycemia. The authors concluded that the higher drug and ambulatory care costs associated with insulin lispro are balanced by lower inpatient costs thereby resulting in cost neutrality compared to human insulin. Cost neutrality combined with better flexibility and potential reductions in hypoglycemia-related hospitalizations suggest that insulin lispro is a viable treatment option without adding overall healthcare costs.(60)

*Chen et al. 2005*

The authors compared medical and pharmacy costs and utilisation between patients with diabetes mellitus who used insulin lispro and those who used human insulin. The research employed a propensity score binning technique to address treatment selection bias. The authors used retrospective cohort design to analyse claims data from a managed care organisation over a 12-month period.

They found that insulin lispro users had higher diabetes-related (+$79) and total pharmacy costs (+$212) compared to human insulin users. However, patients using insulin lispro experienced lower nondiabetes medical costs (-$2,286) thus leading to similar total medical costs between the two groups. Thus, the study highlighted that insulin lispro could provide economic advantages through fewer hospitalizations while delivering health benefits in terms of improved glycemic control.(61)

## 10.2.2 Cost-effectiveness of rapid-acting insulin analogues

Ten studies sought to determine the cost-effectiveness of rapid-acting insulin analogues compared to human insulin for the treatment of T1DM and T2DM.

Eight studies used decision-models to determine the incremental cost-effectiveness ratio. One study used data from a randomised controlled trial to determine the cost-effectiveness of insulin analogues. One study used a bid-up method to determine the maximum willingness-to-pay for insulin analogues and calculate the net-health benefit from this treatment. Four studies included patients with both T1DM and T2DM. Five studies included patients with only T1DM. One study included patients with T2DM only. One study focused specifically on pregnant persons with T1DM. Overall, the quality of evidence ranged from low to high.

*Davey et al 1998*

The authors used a willingness-to-pay (WTP) analysis to evaluate the cost effectiveness of insulin lispro in order to support the addition of the rapid-acting insulin analogue to the Australian national formulary. WTP evaluates benefits in cost-benefit analysis (CBA) which, in turn, represents an absolute decision rule. The study had 83 participants with T1DM and T2DM compare insulin lispro to human insulin. Using a meta-analysis, the study found 92% of patients preferred insulin lispro (listed as insulin A) while 8% preferred neutral insulin (insulin B).(62)

Overall, the study identified adding insulin lispro to the national formulary offered a net benefit to patients.

*Kilburg et al. 2002*

The authors conducted an economic evaluation from the perspective of a third-party payer of treatment with insulin lispro compared with human insulin in adult patients with T1DM and T2DM.

The authors used a Markov model structure with a cycle duration of 3 months to simulate the course of the disease across different levels of care. Patients were assumed to require insulin for treatment intensification, and could receive either insulin lispro or normal insulin. Transition probabilities between states were obtained from a prospective, open-label study by Stocks et al. (1999), which examined the course of treatment in 150 patients with diabetes mellitus that received treatment intensification with human insulin and then switched to insulin lispro.

Costs were derived from a survey of 19 general practitioners and diabetologists. Each clinician retrospectively documented the resource utilisation of two defined patients for each health care level over a period of one year. Costs included medical services, drug costs, costs for medical and assistive devices, costs for specialist visits, hospitalisation costs and laboratory costs. All costs were presented in German marks (DM). The survey showed that, in the primary care setting, the annual cost of treatment per patient was lower with insulin lispro compared to human insulin, but this relationship was inverted in the specialist care setting.

The main outcome of the study was the annual cost of treatment per patient. The results showed that treatment with insulin lispro was cost-saving compared with treatment with human insulin, with an annual reduction in costs of 468 DM. These results were replicated with a survey of 30 general practitioners and diabetologists that were not involved in the initial survey.(63)

*Reviriego et al. 2008*

The authors conducted a retrospective analysis with 100 patients from three Spanish health care centres to assess the costs associated with severe hypoglycemia (SH) in patients with T1DM. They evaluated the cost-effectiveness of insulin lispro compared to human insulin in preventing SH episodes. The research focused on resource utilisation related to SH episodes including both direct and indirect medical costs.

The study reported the average cost per SH episode was €366 where hospitalisation accounted for €183 (about 50% of total costs). They found that insulin lispro users had lower rates of SH episodes compared

to those using human insulin. Incidence rates were 33 and 73 episodes per 100 patients per year for lispro and human insulin respectively. Costs ranged from €277 to €3,853 to prevent one episode of SH using insulin lispro; costs are dependent on patient context.(64)

*Cameron et al. 2009*

The authors used the Center for Outcomes Research Diabetes Model to stimulate long-term diabetes-related complications and costs of various insulin therapy to evaluate the cost-effectiveness of insulin analogues compared to human insulin. They gathered and analysed clinical data from meta-analyses of randomised controlled trials (RCTs) to derive inputs for the model including effects on HbA1c and hypoglycemia rates.

Results showed insulin aspart was more effective and less costly than human insulin for T1DMthereby indicating cost savings. Insulin lispro proved more effective but had an incremental cost of Can$28,996 per quality adjusted life year (QALY). Similarly, long-acting insulin analogue glargine also proved more effective but at higher incremental costs. Insulin aspart showed an incremental cost of Can$22,488 per QALY for T2DM while insulin lispro was much higher at Can$130,865.

The results suggest that insulin analogues provide certain clinical advantages and certain rapid-acting insulin analogues such as aspart can be cost effective for T1DM. Conversely, rapid-acting insulin analogues may not be cost-effective for T2DM. These findings emphasise the need for consideration of economic implications before deciding on insulin therapy regimens.(65)

*Lloyd et al. 2009*

The authors examined and compared cost-effectiveness of insulin aspart and human insulin for managing T1DM among pregnant persons in the United Kingdom. Analysis was based on data from the Insulin Aspart Pregnancy Study Group Trial including persons who were either pregnant or planning to become pregnant and had an HbA1c of 8% or lower. Participants were then randomly received insulin aspart or human insulin as part of the basal-bolus insulin regimen. Treatment effectiveness was evaluated based on the percentage of persons who achieved a live birth at term (≥37 weeks gestation).

72.8% of persons who received insulin aspart experienced live birth at term compared to 60.9% of those who received human insulin. The 11.9% was proven statistically significant. The mean cost per person was £3222 for insulin aspart and £3539 for human insulin. However, the difference was not found to be statistically significant. The analysis showed that insulin aspart was associated with fewer neonatal admissions, contributing to its cost-effectiveness despite not showing a significant cost reduction.

The study concluded that insulin aspart is the dominant treatment option for pregnant persons with T1DM due to the higher rate of live births without increasing treatment costs. The authors recommend further research with a prospective study design to validate these findings.(66)

*Pratoomsoot et al. 2009*

The authors conducted an economic evaluation from the perspective of the National Health Service (NHS) of treatment with insulin lispro compared to human insulin in adult patients with T1DM in the United Kingdom.

The analysis was performed using the CORE Diabetes Model. This model projects long-term health and economic outcomes of a cohort of patients with diabetes. It is based on a series of sub-models simulating major complications of diabetes. Each sub-model is a Markov model using Monte Carlo simulation incorporating time, state, time-in state, and transition probabilities derived from published sources. It accounts for baseline cohort characteristics, history of complications, current and future management of diabetes, concomitant medications, treatment effects and changes in physiological parameters over time. Model output includes complications, life expectancy, quality-adjusted life expectancy, annual costs per patient, cumulative costs per patient, and the incremental cost-effectiveness ratio (ICER).

The authors developed a literature review to identify research on the clinical efficacy of rapid-acting insulin analogues compared with human insulin, and cohort characteristics representative of T1DM patients within the UK. The search was limited to studies in humans, published in English language, and between the years of 1990 and 2008. The search was developed in the PubMed, EMBASE, and Ovid MEDLINE databases.

Baseline cohort characteristics were derived from several studies found on the literature review. Patient demographics, baseline complications, and medical history were obtained from records of primary care physicians in The Health Improvement Network database in the UK. Baseline risk factors (i. e., HbA1c, systolic blood pressure, lipoproteins and triglyceride levels) were derived from T1DM patient records from Newcastle upon Tyne's clinics over a 9-year period. Data on ethnicity within the population were obtained from the Office for National Statistics UK.

Clinical effects of lispro and human insulin were obtained from the results of a meta-analysis. Hypoglycemic event rates specific to insulin lispro were not reported in the meta-analysis, and therefore the rates for rapid-acting insulin analogues in general were used instead. Hypoglycemic event rates were assumed to remain constant over time in both arms. Patients were assumed to remain on the same treatment regimens throughout the simulation, and HbA1c was assumed to follow a progression in both arms based on data from the Diabetes Control and Complications Trial (DCCT).

The study followed the perspective of the NHS, and therefore only direct medical costs were considered. Treatment was defined as a basal-bolus regime using NPH insulin as the basal component in both arms. Prices of insulin NPH (Humulin N), insulin lispro (Humalog), and regular human insulin (Humulin R) were obtained from the Monthly Index of Medical Specialties. The costs of insulins were based on weighted averages of the main insulin products. The annual costs of insulins were calculated based on end-of-trial doses in a study of patients with a diagnosis of T1DM form more than 2 years on established basal-bolus regimens aiming for tight glucose control that compared insulin lispro plus NPH insulin versus human insulin plus NPH insulin. Costs associated with self-monitoring of blood glucose, pharmacy costs, and costs of complications were also included and derived from published sources. All costs were expressed in 2007 currency (GBP).

Health-related quality of life utilities were derived from the United Kingdom Prospective Diabetes Study (UKPDS). All costs and benefits were discounted at a rate of 3.5% per annum. A time horizon of 50 years was used in the base-case analysis. A willingness-to-pay threshold of 30,000 GBP per QALY gained was used to determine the cost-effectiveness of the intervention.

Several sensitivity analyses were conducted. First, the time horizon was adjusted between 0 and 30 years. Second, discount rates for costs and outcomes were applied at 0 and 7% per annum. Third, the efficacy of insulin lispro was modified according to the results of other published studies. Fourth, the rate of severe hypoglycemic events for insulin lispro was applied to both treatment arms, assuming no difference in this outcome. Fifth, the daily dose of insulin was modified. Lastly, a probabilistic sensitivity analysis was developed from 1000 iterations of 1000 patients using non-parametric bootstrapping.

The results for the base-case analysis showed that treatment with insulin lispro dominated that with human insulin, which means that it achieved greater efficacy and was less costly. These results were robust to changes in model parameters in the sensitivity analyses. However, hypoglycemic event rates were the main driver for these results. The probabilistic sensitivity analysis calculated a probability of 83.9% that insulin lispro is cost-effective under the base-case scenario, but it was reduced to 59.1% when the benefit in severe hypoglycemia was abolished.(67)

*Pollock et al. 2011*

The authors conducted an economic evaluation from the perspective of a Japanese third-party healthcare of treatment with insulin aspart compared to human insulin in adult patients with T2DM.

Data on treatment efficacy was obtained from the Nippon Ultra-Rapid Insulin and Diabetic Complication Evaluation-Study (NICE study). This was a 5-year, open-label, randomised controlled trial which compared cardiovascular outcomes in Japanese T2DM patients intensively treated with rapid-acting human insulin (n = 162= or insulin aspart (n = 163). The primary endpoint of the trial was a composite of myocardial infarction, angina pectoris, cerebral infarct, transient ischemic attack, coronary artery bypass graft, or percutaneous coronary intervention. Secondary endpoints included HbA1c levels, postprandial glucose, and fasting plasma glucose concentrations. The study showed a 43% reduction in incidence of the composite primary endpoint in patients on insulin aspart compared with those on human insulin (12.8 events / 1000 person-year vs. 22.2 events / 1000 person-year, $p < 0.02$). For the secondary outcomes, no difference was observed on $HbA1c_{A1c}$ levels or fasting plasma glucose, but a significant decrease in 90-minute postprandial glucose was observed in patients on insulin aspart compared to those on human insulin (142 ± 58 vs. 226 ± 48 mg/dl, $p < 0.02$).

For the cost-effectiveness analysis, the authors used a discrete-time, cohort-level model with an annual cycle length. The model comprised 2 distinct sections. The first used a 5-year time horizon using within-trial outcomes based on complication incidence, mortality, and costs from the NICE study. The second made post-trial projections over a 10-year time horizon using the trial outcomes as baseline and progression formulas from the United Kingdom Prospective Diabetes Study (UKPDS) and a 2007 paper on hypertension and stroke. To address uncertainty in the outcomes, a series of sensitivity analyses

were developed by increasing mortality event rates in the insulin aspart arms in steps of 20%. A willingness-to-pay threshold of JPY 5,000,000 per QALY was used.

Adverse event costs were derived from hospital receipt data supplied by the Japanese Medical Data Centre in 2008 Japanese yen (JPY). For severe hypoglycemia, a value of € 239 was used from the study by Reviriego et al. (2008), and converted to JPY using the mid-2008 exchange rate (167.6 JPY to 1 euro). Costs of concomitant medications were not considered, since inter-arm differences in medication use were not statistically significant in the NICE study.

The main outcome was the total net health benefit, which was calculated as the difference between the change in quality-adjusted life expectancy and the quality-adjusted life expectancy value. The latter was obtained by dividing the change in costs over the willingness-to-pay threshold.

The results of the analysis showed that insulin aspart was cost-saving (i. e., more effective and less costly) over the 5-year duration of the NICE study. Over the projected 10-year horizon, insulin aspart was also the dominant intervention, projected to save an average of JPY 252,923 per patient. The efficacy-based sensitivity analysis showed that insulin aspart remained cost-effective up to the point where only 18% of the benefit observed in the NICE study remained. Other sensitivity analyses showed that model outcomes were robust to changes in input parameters.(68)

*Cazarim et al. 2017*

The authors conducted an economic evaluation from the perspective of the Brazilian Public Health System of insulin analogues compared to human insulin in adult patients with diabetes mellitus. For this review, we will only present the methods and results for rapid-acting insulin analogues and human insulin.

The study followed the perspective of the Brazilian Public Health System, and therefore only direct medical costs were considered. The cost of treatment for each insulin was obtained by multiplying the cost per IU by the mean daily dose recommended, and calculated per patient per year. The calculations assumed 360 days in a year and a body weight of 70 kg. Mean dose values were extracted from a meta-analysis by Sanches et al. (2013). Costs were extracted from the Market of Regulation of the Market of the Market of Medicines, considering the government procurement price and a tax rate of 18%. All costs were recorded in Brazilian currency (BRL) and referred to the month of June 2016. The following insulin formulations were considered: regular human insulin (INSUNORM R, Aspen Pharma, 100 IU / mL, 10 mL injectable solution), insulin aspart (NOVORAPID, Novo Nordisk, 100 IU / ml, 10 mL injectable solution), and insulin lispro (HUMALOG, Eli Lilly, 100 IU / mL, 10 mL injectable solution).

Data related to the reduction of HbA1c were obtained from the same meta-analysis by Sanches et al. (2013), and were used to compare treatment with regular human insulin and insulin analogues. Insulin glulisine was excluded from the analysis because it was not analysed in the meta-analysis.

The authors used a decision tree model to compare the interventions. They created different scenarios to capture the variation of costs and reduction of HbA1c with each type of insulin. The results were

summarised in an incremental cost-effectiveness ratio (ICER). The willingness-to-pay threshold was defined as 3 times the GDP per capita for Brazil in 2015.

The results of the base-case scenario calculated an ICER for fast-acting insulin analogues of 3.005.69 BRL (insulin aspart) and 11,461.25 BRL (insulin lispro) compared to regular human insulin. In the best-case scenario (i. e., minimum cost difference and maximum effectiveness), the ICER was lower at 1,768.59 BRL (insulin aspart) and 3,308.54 BRL (insulin lispro). In the worst-case scenario (i. e., minimum effectiveness and maximum cost differences), both insulin analogues were dominated by regular human insulin, meaning that they were more costly and less effective.(69)

*Valentine et al. 2018*

The authors conducted an economic evaluation from the perspective of a German healthcare payer of rapid-acting insulin analogue compared to human insulin in adults with T1DM.

This cost-effectiveness analysis was developed using the PRIME Diabetes Model. This model is a modular, patient-level, discrete event simulation model that incorporates clinical data from patients with T1DM. It incorporates data from large-scale trials and database analyses and makes use of model averaging and multi-models to incorporate as much available clinical data as possible. In addition, the model includes covariance of patient characteristics and risk factor progression based on an analysis of patient-level data from the Diabetes Control and Complications Trial (DCCT). Model outputs include life expectancy, quality-adjusted life expectancy, cumulative incidence of complications, evolution of risk factors, costs, and an incremental cost-effectiveness ratio (ICER).

The authors conducted a structured literature search in PubMed, EMBASE, and the Cochrane Library to identify clinical trials and meta-analyses published between January 1, 2006 and January 1, 2015 that provided data on the efficacy of rapid-acting insulin analogue compared to human insulin in patients with T1DM. They chose this time period to exclude data that would not represent current routine clinical practice. The meta-analyses and clinical trials identified reported that rapid-acting insulin analogues lowered HbA1c and the rates of severe and nocturnal hypoglycemia compared with human insulin. Other risk factors were assumed to have no difference from rapid-acting insulin analogues.

Furthermore, the literature search identified 2 relevant studies that provided most baseline cohort characteristics of German T1DM populations for the model. The authors extracted the remaining characteristics (i. e. Body mass index) from a comparable European cohort that was matched for age and diabetes duration. In addition, they included data indexed by sex and age from German life tables from the World Health Organization to capture the risk of baseline mortality. The authors created an artificial cohort of 100,000 patients in both arms for the analysis.

The analysis was conducted from the perspective of a German healthcare payer. Therefore, only direct medical costs were considered. All costs were reported in 2015 Euros. Treatment with insulin was assumed as a combination of basal and bolus insulin. Insulin costs were taken from the 2015 Rote Liste. For the insulin bolus component, rapid-acting insulin lispro (Humalog, Eli Lilly) was compared to human insulin. The basal component of treatment was assumed to be NPH insulin in both arms, because it was

the most widely single insulin in a German survey. Costs associated with diabetes-related complications, concomitant medications, and adverse events were taken from published sources for the German setting.

Health state utilities were informed by a systematic literature review to identify data specific to populations with T1DM. Both costs and clinical benefits were discounted at a rate of 3% per annum. A hypothetical willingness-to-pay threshold of € 30,000 per QALY gained was used in the analysis. The base-case scenario was conducted over a 50-year time horizon to capture the onset of late-stage complications. A probabilistic sensitivity analysis was developed by performing 1000 non-parametric bootstrapping of 2000 patients per group. Costs and utilities were assumed to have a standard deviation of 20% and lognormal distribution.

Various scenario analyses were performed. First, NPH insulin was changed to insulin glargine as the basal component of treatment. Second, the base-case multiplicative approach to quality-of-life utility coalescing was combined with a diminishing utility model. Third, rapid-acting insulin analogues were assumed to have no effect on HbA1c levels. Fourth, rapid-acting insulin analogues were assumed to have no effect on hypoglycemia rates. Lastly, all patients were assumed to trend towards an $HbA1c_c$ target of 7.0% over a 15-year period.

The results for the base-case analysis showed an ICER of € 4,490 per QALY gained for rapid-acting insulin analogues compared to human insulin. Probabilistic sensitivity analysis demonstrated that the results were insensitive to changes in model parameters, with a median ICER of € 4,974 per QALY gained that was below the willingness-to-pay threshold in all bootstrapped cohorts.

Scenario analyses demonstrated that the main driver for improved quality-adjusted life expectancy and cost-effectiveness was the reduced hypoglycemia rates associated with rapid-acting insulin analogue. The scenario where rapid-acting insulin analogues were assumed to have no benefit on hypoglycemia rates produced an ICER of € 74,622 per QALY gained The ICER in other scenario analyses was kept below the willingness-to-pay threshold.(70)

*Nosrati et al. 2023*

The authors conducted an economic evaluation of insulin analogues compared with human insulins for treating adult patients with T1DM and T2DM from the perspective of the Iranian healthcare system. For the purpose of this submission, we will focus on the part of the study related to rapid-acting insulin analogues.

They performed a systematic search on Pubmed, MEDLINE, Scopus, and Web of Science to extract clinical and economic data of the treatment with insulin aspart and human insulin in both T1DM and T2DM. The search was limited to systematic review and meta-analysis articles published in English. They retrieved data on the effect of both treatments on HbA1c levels, hypoglycemic events (severe, nocturnal, and overall hypoglycemia), and weight gain.

They adopted the perspective of the Iranian healthcare system. Therefore, only direct medical costs were included. These included costs of insulin therapy (calculated according to the national drug prices and unit-per-weight dosing regimes), costs of insulin administration (e. g. needles), and costs of management of hypoglycemic events. It was assumed that non-severe hypoglycemic events were treated by patients themselves and did not induce any costs on the healthcare system. The cost of concomitant medications (e. g. lipid-lowering agents, other antidiabetics), were assumed to be equal in both arms. All costs were calculated in US dollars (USD) in 2022, using a currency exchange rate of 270,000 Iran Rial (IRR) to 1 USD.

For T1DM, the authors reported a cost-effectiveness ratio to represent the additional healthcare costs needed to obtain a 1% reduction in HbA1c levels. For T2DM, they conducted a cost-minimization analysis, comparing the cost of treatment from both interventions under the assumption that the effects of both drugs were equal. The time horizon was set at 1 year. No sensitivity analyses were performed.

The results showed that treatment of patients with T1DM with insulin aspart was more effective (and more costly) than treatment with human insulin, with an incremental cost-effectiveness ratio of $83 USD per 1% reduction in HbA1c levels per patient per year. However, the authors didn't use a willingness-to-pay threshold to determine whether the intervention was cost-effective in the local setting. For patients with T2DM, the authors concluded that human insulin was the preferred treatment due to the lower associated costs compared with insulin aspart.(71)

## 10.2.3. Price surveys of rapid-acting insulin analogues

Seven articles compared the price of human insulin with that of rapid-acting insulin analogues in different markets. Six studies used cross-sectional surveys to extract data on insulin prices. 1 study conducted a longitudinal, retrospective price survey. 5 studies obtained price data from a single country. Two studies provided cross-country price comparisons. Overall, the studies provide information on insulin prices from 6 high-income countries (Australia, France, Latvia, Russia, the United Kingdom, the United States), 6 upper-middle-income countries (Brazil, China, El Salvador, Indonesia, Iran, South Africa), 10 lower-middle-income countries (Bangladesh, Ghana, India, Jordan, Kenya, Kyrgyzstan, Morocco, Pakistan, the Philippines, Tanzania), and e low-income country (Ethiopia, Mali, Uganda).

All included studies used observational research methods. The quality of the evidence ranged from low to very low.

*Ewen et al. 2019*

The authors conducted a cross-sectional survey on evidence price and availability of insulin in 13 countries in 2016.

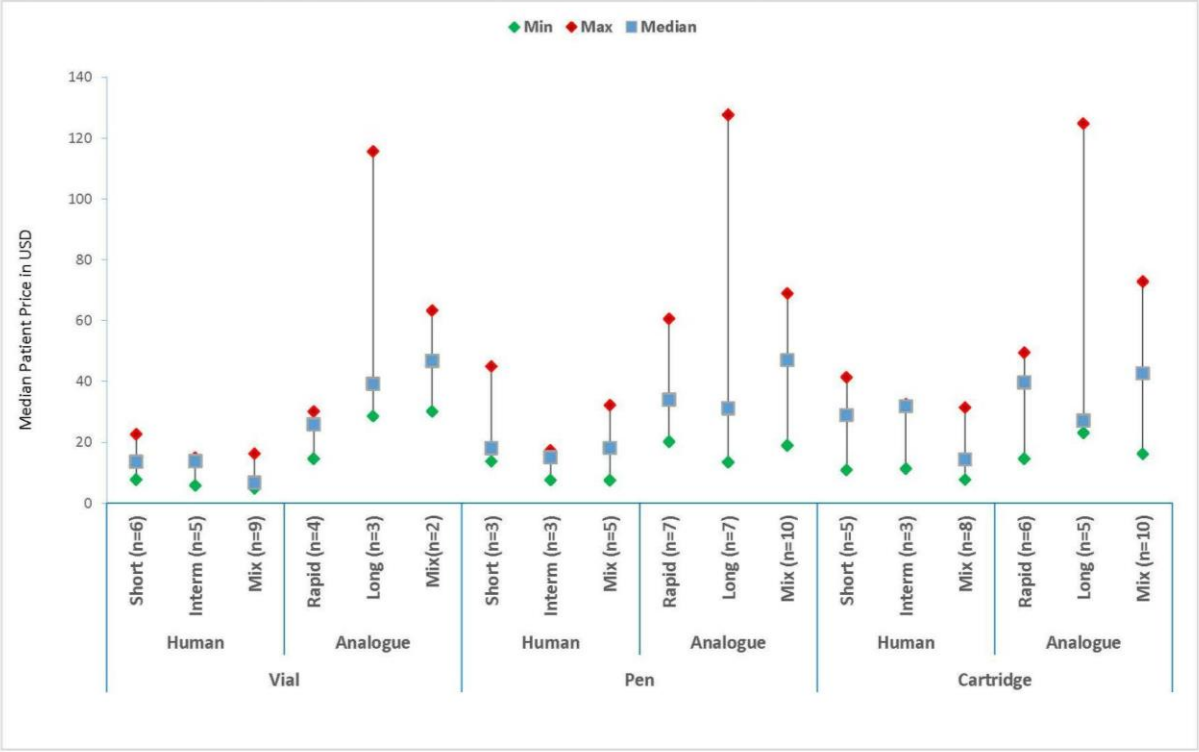
The countries included Brazil, China (Hubei and Shaanxi provinces), Ethiopia, Ghana, India (Haryana and Madhya Pradesh states), Indonesia, Jordan, Kenya, Kyrgyzstan, Mali, Pakistan, Russia (Kazan province) and Uganda. Data were collected from 3 sectors (i. e., public hospitals, private retail pharmacies, and private hospitals / clinics) and in 3 areas (i. e., the capital or major urban city, the province closest to said

city with the largest provincial hospital, and the district closest to the province with the largest district hospital) per survey. In each area, the sample included the largest public hospital, the largest private hospital / clinic, and 5 private retail pharmacies. These pharmacies were selected at random from those within 5 km of the public hospital.

The main outcome was price and availability of insulins. Insulin prices were standardised to 10 mL of 100 IU / mL and converted to US dollars. For each survey, median prices for each insulin category, type, and presentation were assessed per outlet and per sector. The government procurement prices were collected from the national procurement office, central medical stores, or from the public hospitals surveyed.

The results are presented as minimum, maximum and median price per presentation per insulin category in the figure below (courtesy of Dr. Margaret Ewen).(72)

## *Figure 2. Median prices of insulin by category and sector, 10 mL 100 IU/mL in USD*




*n = number of surveys*

*Wineinger et al. 2019*

The authors conducted a retrospective, longitudinal survey on drug prices in the United States from January 1, 2012 through December 31, 2017. We will only discuss the methods and results related to rapid acting insulin and insulin analogues in this review.

The authors obtained prescription-level pharmacy claims from the Blue Cross Blue Shield (BCBS) Axis database. This database includes administrative claims data from independent companies representing more than 35 million individuals with private pharmaceutical insurance in the United States. BCBS Association employees supported access to data but were not involved in the analysis or publication decisions. Data was limited to top-selling branded prescription drugs of 2017, defined on the basis of total sales exceeding 500 million USD in the United States or 1 billion USD worldwide. Additionally, drugs that are administered in a clinical setting or not distributed through a pharmacy were omitted.

The primary outcome of the study was the total price paid from each claim. This price represented the out-of-pocket cost paid by the individual plus the cost paid by the insurer. Median costs for the prescriptions were summarised in each calendar month. Relative price changes were found by calculating the difference in median costs between 2 dates and scaling this difference by the preceding date's median cost.

The results showed that the increase in price over the 6 year period was 117% for human insulin (Humulin), 117% for insulin lispro (Humalog), and 118% for insulin aspart (Novolog). The median cost over the study period for insulin products is presented in the table below.

***Table 7. Median monthly cost of rapid-acting insulins in USD(73)***

| 2012 | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Humulin | 67 | 67 | 67 | 67 | 67 | 67 | 68 | 73 | 73 | 73 | 73 | 73 |
| Humalog | 126 | 126 | 126 | 126 | 126 | 126 | 132 | 134 | 134 | 134 | 134 | 134 |
| Novolog | 244 | 244 | 244 | 244 | 244 | 244 | 244 | 263 | 263 | 263 | 263 | 264 |
| 2013 | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec |
| Humulin | 78 | 78 | 78 | 78 | 78 | 83 | 85 | 85 | 85 | 85 | 84 | 86 |
| Humalog | 144 | 144 | 144 | 144 | 144 | 144 | 144 | 157 | 157 | 157 | 157 | 165 |
| Novolog | 281 | 281 | 281 | 281 | 281 | 281 | 282 | 304 | 303 | 303 | 304 | 333 |
| 2014 | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec |
| Humulin | 92 | 92 | 92 | 92 | 92 | 95 | 100 | 100 | 100 | 100 | 100 | 110 |
| Humalog | 172 | 172 | 172 | 171 | 171 | 187 | 188 | 188 | 188 | 188 | 189 | 207 |
| Novolog | 332 | 332 | 332 | 331 | 332 | 364 | 364 | 364 | 364 | 364 | 367 | 400 |
| 2015 | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec |
| Humulin | 105 | 110 | 110 | 110 | 110 | 121 | 121 | 121 | 121 | 121 | 121 | 129 |
| Humalog | 204 | 204 | 204 | 204 | 204 | 224 | 224 | 224 | 224 | 224 | 224 | 238 |
| Novolog | 399 | 399 | 399 | 399 | 403 | 439 | 439 | 439 | 439 | 439 | 439 | 465 |
| 2016 | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec |
| Humulin | 128 | 128 | 128 | 128 | 128 | 128 | 130 | 138 | 138 | 138 | 138 | 137 |
| Humalog | 238 | 238 | 238 | 238 | 238 | 238 | 243 | 255 | 255 | 255 | 255 | 255 |
| Novolog | 462 | 462 | 462 | 462 | 462 | 462 | 495 | 498 | 498 | 498 | 498 | 498 |
| 2017 | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec |
| Humulin | 137 | 136 | 136 | 136 | 138 | 145 | 147 | 146 | 146 | 146 | 146 | 146 |
| Humalog | 254 | 254 | 254 | 254 | 274 | 274 | 274 | 274 | 274 | 274 | 274 | 274 |
| Novolog | 494 | 494 | 532 | 532 | 532 | 532 | 532 | 532 | 532 | 532 | 532 | 532 |

Humalog: insulin lispro; Humulin: human insulin; Novolog: insulin aspart.

*Phulpagare et al. 2021*

The authors conducted a cross-sectional survey on the cost variation of insulin products in India from January 15 to February 15, 2020. For this submission, only data on the cost of rapid-acting insulin and insulin analogues will be discussed.

The authors collected data from official websites of the Current Index of Medical Specialties, the National Pharmaceutical Pricing Authority, and the Government of India. All insulin preparations manufactured by more than one company were considered. Only the price of insulin dispensed in vials was collected. Unit prices were expressed as cost per 10 mL in Indian Rupee (INR). The percentage cost variation for each product was calculated as the ratio of the highest to lowest cost brand of the same insulin preparation.

The study analysed the cost of 116 insulin formulations. Data on rapid-acting insulin and insulin analogues are presented in a table below.(73)

### *Table 8: Minimum and maximum prices, and cost variation of rapid acting insulin products(73)*

| Insulin preparation | Maximum price (INR) | Minimum price (INR) | Cost variation (%) |
|---|---|---|---|
| Insulin (Analogue) Aspart - 100 IU | 1952.00 | 1837.00 | 6.26 |
| Insulin (Highly Purified) - 40 IU | 185.38 | 90.00 | 105.98 |
| Insulin (Highly Purified) - 400 IU | 113.37 | 78.52 | 44.38 |
| Insulin (Human) - 40 IU | 154.66 | 140.70 | 9.92 |
| Insulin (Human) - 100 IU | 490.00 | 390.00 | 25.64 |
| Insulin (Human Recombinant) - 40 IU | 154.20 | 143.43 | 7.51 |

*Saeed et al. 2022*

The authors conducted a cross-sectional survey from September to December 2019 to determine the prices, availability, and affordability of insulin and five comparator medicines in Pakistan. For the purpose of this review, we will focus on the methods and results related to pricing of regular human insulin and analogue insulins.

The authors selected facilities from both public and private sectors in each of the eight cities included (namely Islamabad, Lahore, Bahawalpur, Abbotabad, Peshawar, Karachi, Quetta, and Muzaffarabad). In each city, the biggest hospital was selected as a survey anchor. The remaining facilities in each city were selected at random for the survey, and included 4 other hospitals, 1 private pharmacy within 10 km from each public sector hospital, and 40 private- and 40 public-sector medicine outlets.

Data were collected for every unique insulin product, irrespective of the manufacturer, found at a given medicine outlet. Unique products were identified by their brand name, type, strength, and presentation. The data collection form included data on brand and generic names of medicines, dosage form, strength, primary packing, pack size, manufacturer, the patient price for the whole pack, and unit price.

This form was pilot tested in a big private-sector retail pharmacy before final data collection. Data were validated by re-conducting the survey in one private pharmacy selected at random. Prices were obtained from private pharmacies only because these medicines are given for free in the government sector.

The survey found 320 insulin products (including duplicates) in the Pakistani market, from which 40 were manufactured locally and 280 by foreign multinational companies. Minimum, maximum, and median prices are presented in a table below both in Pakistani rupees (PKR) and US dollars (USD). The median prices of biosimilar rapid-acting insulin analogues were not available because these products were not found in the private sector.(74)

### *Table 9. Minimum, maximum, and median unit prices of insulin products(74)*

| Insulin product | Maximum price (PKR / USD) | Median price (PKR / USD) | Minimum price (PKR / USD) |
|---|---|---|---|
| Rapid acting human, OB | 869.80 / 5.40 | 868.90 / 5.40 | 608.10 / 3.80 |
| Rapid acting human, BS | 4323.30 / 26.90 | 610.00 / 3.80 | 457.00 / 2.80 |
| Aspart, OB | 3070.00 / 19.10 | 3010.30 / 18.70 | 2913.30 / 18.10 |
| Glulisine, OB | 2764.00 / 17.20 | 2626.60 / 16.30 | 2626.60 / 16.30 |
| Lispro, OB | 3968.30 / 24.70 | 2300.00 / 14.30 | 1020.40 / 6.30 |

* BS: biosimilar; OB: Originator brand

*Zarei et al. 2022*

The authors conducted a cross-sectional study assessing the affordability of all registered medications to treat T1DM and T2DM in Iran's healthcare system in 2017. For the purpose of this submission, we will only present data on the price of human insulin and insulin analogues.

The authors developed a structured form to collect medicine information (i. e., generic name, ATC code, dosage forms, dose, defined daily dose, market availability, price, insurance coverage, consumption duration, consumption interval) from formal websites such as WHO, Iran FDA, Iranian Health Insurance Organization, and Ministry of Cooperatives, Labor and Social Welfare.

The results of the medicine price are presented in a table below. They represent the lowest price of generic medicine in Iranian Rial.(75)

## *Table 10. Diabetes medication in Iran Drug List in 2017(75)*

| Medicine Name | ATC code | Price in RI |
|---|---|---|
| Insulin (regular) | A10AB01 | 140 000 |
| Insulin aspart | A10AB05 | 295 000 |
| Insulin glulisine | A10AE01 | 235 000 |

*Barber et al. 2024*

The authors conducted an economic evaluation to determine a sustainable cost-price for antidiabetic medications and compare it to the lowest reported prices in 12 countries. For the purpose of this review, only the methods and results related to human insulin and rapid-acting insulin analogues will be discussed.

Cost-based prices (CBPs) were defined as prices that would be expected in competitive markets to provide manufacturers with sustainable returns while avoiding excessive profit margins. Costs of medicine manufacture were calculated by adding the cost of the active pharmaceutical ingredient (API), the costs of formulation and secondary packaging, logistical costs, profits, and taxes. Average API prices were estimated using a weighted least-squares regression model of international API shipment data from January 1, 2016 to March 31, 2023, Such data was available from a trade database, and was supplemented with direct solicitation from manufacturers. Costs of specialised injection devices were derived from interviews with industry experts. A range of CBPs was produced by changing the assumptions on production volumes and / or higher operating or profit margins.

Market prices were collected for 12 countries from public databases. The results included 4 high-income countries (i. e., France, Latvia, the United Kingdom, and the United States) and 8 middle-income countries (Bangladesh, Brazil, China, El Salvador, India, Morocco, the Philippines, and South Africa). These countries were chosen based on the availability of data on prices and to provide geographic and economic diversity in the sample. For each country, the lowest price identified for each medicine and each formulation was reported.

The results demonstrated that the lowest market prices were higher than the cost-based prices for most insulin products. The comparison of prices is depicted in the table below.

## *Table 11. Cost per month(27)*

| Medicine | Cost-based price in USD | Lowest market price in surveyed countries in USD |
|---|---|---|
| Human Insulin | | |
| Vial | 2.37-5.94 | 1.93-198.90 |
| Cartridge | 3.00-9.13 | 10.62-53.27 |
| Pre-filled pen | 4.69-29.44 | 9.37-31.73 |
| Insulin aspart | | |
| Vial | 4.86-10.59 | 19.42-208.35 |
| Cartridge | 5.39-13.61 | 13.95-256.65 |
| Pre-filled pen | 7.08-33.92 | 25.48-268.20 |
| Insulin lispro | | |
| Vial | 4.87-10.62 | 25.18-118.65 |
| Cartridge | 5.40-13.63 | 25.04-488.55 |
| Pre-filled pen | 7.09-33.94 | 26.71-152.70 |
| Insulin glulisine | | |
| Vial | 4.79-10.47 | 21.47-407.70 |
| Cartridge | 5.33-13.49 | 21.24-50.64 |
| Pre-filled pen | 7.02-33.81 | 23.51-526.95 |

*Bayat et al. 2024*

The authors conducted a quantitative, descriptive, cross-sectional study on availability and pricing of insulin in South Africa in March 2023. For the purpose of this review, only data about the pricing of insulin analogues will be discussed.

The study population consisted of all public and private sector pharmacies and dispensaries in South Africa The sample size was calculated at 234 with a 5% type-I error and an 80% response distribution. From the 4496 pharmacies that were invited to participate in the study, 254 pharmacies consented to do so. Data was collected from all included pharmacies via an online survey.

The list of insulins were extracted from the 22nd WHO EML, the 2020 edition of the South African Standard Treatment Guidelines and Essential Medicines List, and the South African Health Products Regulatory Authority. This produced a total of 18 insulins that were selected for the study.

The price of insulin was the actual price paid by the patient or the government procurement price. The government procurement price was extracted from the National Department of Health's Master Health Product list. The final unit price of each insulin in the private sector was determined as the selling price inclusive of 15% value added tax and the maximum dispensing fee.

Prices of insulin were also collected from a basket of countries to allow for an international price comparison. The actual prices paid and the government procurement price were compared to the national insulin prices from the Australia Pharmaceutical Benefit Scheme, together with the United Kingdom's British National Formulary, the United States' Center for Medicare & Medicaid Services and 3 of the countries included in the AFRO Essential Medicines Price Indicator (Kenya, Tanzania and Ghana). To compare these international prices, all prices were converted to the US dollar on the last day of data collection.

The results about pricing and international price comparison were only available for 1 rapid-acting insulin analogue(i. e. insulin glulisine). The table below shows available prices for insulin glulisine compared to human insulin in all countries included.

### *Table 12. International price comparison in USD(76)*

| | US | UK | Australia | African countries | SA GPP | SA SEP (excl. VAT) | SA SEP (incl. VAT) | SA MPR* |
|---|---|---|---|---|---|---|---|---|
| Regular Rapid-Acting | 131.20 | 18.82 | 19.00 | 4.21 | 1.89 | 15.63 | 18.39 | 24.37 |
| Insulin Glulisine | n/a | 18.20 | 22.54 | n/a | n/a | 18.65 | n/a | 30.40 |

Adapted from Bayat et al. 2024.
GPP: Government Procurement Price; MPR: Medicine Price Registry; SA: South Africa; SEP: Single Exit Price by manufacturer; UK: United Kingdom; US: United States; VAT: Value Added Tax
* Maximum Unit Price

## 10.3 Summary of available data on comparative cost and cost effectiveness of the medicine

Rapid acting insulin analogues are more expensive compared to human insulin across various settings, although production costs remain relatively similar. The growing availability of biosimilars' offers opportunities for price reductions. Despite the higher upfront costs, insulin analogues may result in lower overall health care costs due to a reduced incidence of complications such as hypoglycemia, fewer hospitalizations, and lower rates of diabetes-related complications. These outcomes make the total cost of diabetes treatment with insulin analogues comparable or even lower in the long term.

Cost-effectiveness studies using ICERs across various settings demonstrate that rapid-acting insulin analogues can be cost-effective, especially for T1DM. For T2DM, the cost-effectiveness of insulin analogues is more variable with some studies suggesting they may not be as cost-effective for T2DM as for T1DM.

Survey data from various countries show significant variation in the prices of rapid-acting insulin analogues. While insulin analogues are often more expensive than human insulin, the availability of biosimilars and efforts in price negotiations may help lower costs in the future. Prices of rapid-acting insulin analogue range widely between HICs and LMICs. In HICs like the United States, insulin prices have risen substantially. In LMICs, prices vary with some countries keeping analogue prices relatively close to that of human insulin, while others face significant price disparities.

With the recent success of price reduction policies, we suggest that adding rapid-acting insulin analogues to the EML can hold a reasonable expectation that product prices will reduce in the near future. Updated studies are crucial to achieving availability and accessibility.

# Section 11: Regulatory status, market availability and pharmacopoeial standards

Regulatory status, approved indications, market availability, and pharmacopoeial standards are summarised in the tables below.

## 11.1 Regulatory status and market availability

***Table 13. Approved products for rapid-acting insulin analogues in selected jurisdictions***

| Jurisdiction | Insulin lispro | Insulin aspart | Insulin glulisine |
|---|---|---|---|
| United States(77) | 3 | 2 | 1 |
| EMA(78) | 3 | 2 | 1 |
| Japan(79) | 2 | 4 | 1 |
| Canada(80) | 1 | 4 | 1 |
| Australia(81) | 3 | 2 | 1 |

### *Table 14. Approved indications for rapid-acting insulin analogues in selected jurisdictions*

| Jurisdiction | Insulin lispro | Insulin aspart | Insulin glulisine |
|---|---|---|---|
| United States(77) | "improve glycemic control in adults and children with diabetes mellitus" | "improve glycemic control in adults and children with diabetes mellitus" | "improve glycemic control in adults and children with diabetes mellitus" |
| EMA(78) | "Indicated for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above." | "Indicated for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above." | "Indicated for treatment of adults, adolescents and children, six years or older with diabetes mellitus, where treatment with insulin is required." |
| Japan(79) | "Drugs with a new active ingredient indicated for the treatment of diabetes mellitus where insulin therapy is indicated." | "Drugs with a new active ingredient indicated for the treatment of diabetes mellitus where insulin therapy is indicated." | "Drugs with a new active ingredient indicated for the treatment of diabetes mellitus where insulin therapy is indicated." |
| Canada(80) | "Are indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. HUMALOG insulins are also indicated for the initial stabilisation of diabetes mellitus." | "Are indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis." | "Is indicated for the treatment of adult patients with Type 1 or Type 2 diabetes mellitus where treatment with insulin is required." |
| Australia(81) | "For the treatment of patients with Type 1 (IDDM) and Type 2 (NIDDM) diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis." | "For the treatment of patients with Type 1 (IDDM) and Type 2 (NIDDM) diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis." | "Apidra is indicated for the treatment of type 1 and type 2 diabetes mellitus in adults and children of 4 years or above who require insulin for the control of hyperglycaemia." |

### 11.1.1 Biosimilars

The expiration of patents and advocacy for biosimilar (BS) insulins has encouraged market entry of follow-on biologics in several countries.

***Table 15. Approved products for rapid-acting biosimilar insulin analogues in selected jurisdictions***

| Jurisdiction | Insulin lispro BS | Insulin aspart BS | Insulin glulisine BS |
|---|---|---|---|
| United States(77) | 1 | 0 | 0 |
| EMA(78) | 1 | 2 | 0 |
| Japan(79) | 1 | 1 | 0 |
| Canada(80) | 1 | 2 | 0 |
| Australia(81) | 0 | 1 | 0 |

### *Table 16. Approved indications for rapid-acting biosimilar (BS) insulin analogues in selected jurisdictions*

| Jurisdiction | Insulin lispro BS | Insulin aspart BS | Insulin glulisine BS |
|---|---|---|---|
| United States(77) | "A short-acting human insulin analog indicated to improve glycemic control in adult and paediatric patients with diabetes mellitus." | N/A | N/A |
| EMA(78) | "For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis."<br><br>"This is a biosimilar medicine, which is a biological medicine highly similar to another already approved biological medicine called the 'reference medicine'. For more information, see Biosimilar medicines." | Insulin aspart Sanofi and Kirsty is indicated for the treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.<br><br>"This is a biosimilar medicine, which is a biological medicine highly similar to another already approved biological medicine called the 'reference medicine'. For more information, see Biosimilar medicines." | N/A |
| Japan(79) | "Follow-on biologics indicated for the treatment of diabetes mellitus in cases where insulin therapy is indicated." | "Follow-on biologics indicated for the treatment of diabetes mellitus in cases where insulin therapy is indicated." | N/A |
| Canada(80) | "[1] the biosimilar and the reference biologic drug are highly similar; and [2] there are no clinically meaningful differences in efficacy and safety between the biosimilar and the reference biologic drug" | "[1] the biosimilar and the reference biologic drug are highly similar; and [2] there are no clinically meaningful differences in efficacy and safety between the biosimilar and the reference biologic drug" | N/A |
| Australia(81) | N/A | "Treatment of diabetes mellitus." | N/A |

## 11.2 Pharmacopoeial Standards

### *Table 17. Availability of pharmacopoeial standards*

| | International Pharmacopoeia (82) | United States Pharmacopoeia (83) | European Pharmacopoeia (84) | British Pharmacopoeia (85) |
|---|---|---|---|---|
| Insulin lispro | No | Yes | Yes | Yes |
| Insulin aspart | No | Yes | Yes | Yes |
| Insulin glulisine | No | Yes | Yes | Yes |

## Section 12: Reference list


1. Melo KFS, Bahia LR, Pasinato B, Porfirio GJM, Martimbianco AL, Riera R, et al. Short-acting insulin analogues versus regular human insulin on postprandial glucose and hypoglycemia in type 1 diabetes mellitus: a systematic review and meta-analysis. Diabetol Metab Syndr. 2019 Jan 3;11:2.

2. Eledrisi M, bn-Mas'ud Danjuma M. Comparison of Insulin Analogs and Human Insulins: A Narrative Review. J Diabetes Endocr Pract. 2023;7:10.

3. NICE Clinical Knowledge Summaries (CKS). Insulin therapy in type 1 diabetes: Scenario: Insulin therapy - type 1 diabetes [Internet]. NICE (National Institute for Health and Care Excellence); 2023. Available from: (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

4. Berget C, Messer LH, Forlenza GP. A Clinical Overview of Insulin Pump Therapy for the Management of Diabetes: Past, Present, and Future of Intensive Therapy. Diabetes Spectr Publ Am Diabetes Assoc. 2019 Aug;32(3):194.

5. Insulin Manufacturer to Finally Lower Prices in the US | Human Rights Watch [Internet]. 2023 [cited 2024 Oct 26]. Available from: https://www.hrw.org/news/2023/03/01/insulin-manufacturer-finally-lower-prices-us

6. Dickson S, Gabriel N, Gellad WF, Hernandez I. Estimated Changes in Insulin Prices and Discounts After Entry of New Insulin Products, 2012-2019. JAMA Health Forum. 2023 Jun 16;4(6):e231430.

7. Feldman WB, Rome BN. The Rise and Fall of the Insulin Pricing Bubble. JAMA Netw Open. 2023 Jun 14;6(6):e2318074.

8. Understanding Insulin Market Dynamics in Low and Middle Income Countries - IQVIA [Internet]. [cited 2024 Oct 26]. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/understanding-insulin-market-dynamics-in-low-and-middle-income-countries

9. Gotham D, Barber MJ, Hill A. Production costs and potential prices for biosimilars of human insulin and insulin analogues. BMJ Glob Health. 2018 Sep 25;3(5):e000850.

10. Beran D, Ewen M, Laing R. Constraints and challenges in access to insulin: a global perspective. Lancet Diabetes Endocrinol. 2016 Mar 1;4(3):275–85.

11. Beran D, Gale EAM, Yudkin JS. The insulin market reaches 100. Diabetologia. 2022 Mar 11;65(6):931.

12. T1International Comment on Application to Add Long-acting Insulin Analogues to WHO EML [Internet]. [cited 2024 Oct 21]. Available from: https://www.t1international.com/blog/2021/06/17/t1international-comment-application-add-long-acting-insulin-analogues-who-eml/

13. Akil AAS, Yassin E, Al-Maraghi A, Aliyev E, Al-Malki K, Fakhro KA. Diagnosis and treatment of type 1 diabetes at the dawn of the personalized medicine era. J Transl Med. 2021 Apr 1;19:137.

14. WHO prioritizes access to diabetes and cancer treatments in new Essential Medicines Lists

[Internet]. [cited 2024 Oct 21]. Available from: https://www.who.int/news/item/01-10-2021-who-prioritizes-access-to-diabetes-and-cancer-treatments-in-new-essential-medicines-lists

15. Chan JCN, Lim LL, Wareham NJ, Shaw JE, Orchard TJ, Zhang P, et al. The Lancet Commission on diabetes: using data to transform diabetes care and patient lives. The Lancet. 2020 Dec;396(10267):2019–82.

16. New WHO Essential Medicines List Includes Controversial Insulin Analogues; Recommends Action On High Medicines Prices - Health Policy Watch [Internet]. 2021 [cited 2024 Oct 21]. Available from: https://healthpolicy-watch.news/who-essential-medicines-insulin-analogues/

17. Allocati E, Gerardi C. EFFICACY AND SAFETY OF SWITCHING AMONG HUMAN INSULINS, INSULIN ANALOGUES, AND THEIR BIOSIMILARS IN PATIENTS WITH DIABETES: A SYSTEMATIC REVIEW REPORT NOVEMBER 2020. Final Rep.

18. Ogle GD, Gregory GA, Wang F, Robinson TI, Maniam J, Magliano DJ, et al. The T1D Index: Implications of Initial Results, Data Limitations, and Future Development. Curr Diab Rep. 2023 Oct 1;23(10):277–91.

19. Ali L, Alhassan M. Challenges in achieving adequate glycemic control among children with type 1 diabetes mellitus in a resource-limited setting: A cross-sectional study from Sudan. Diabetes Res Clin Pract. 2024 Feb;208:111113.

20. Vergès B. Cardiovascular disease in type 1 diabetes: A review of epidemiological data and underlying mechanisms. Diabetes Metab. 2020 Nov 1;46(6):442–9.

21. Gregory GA, Robinson TIG, Linklater SE, Wang F, Colagiuri S, de Beaufort C, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol. 2022 Oct 1;10(10):741–60.

22. Diabetes mellitus type 1 - Level 4 cause | Institute for Health Metrics and Evaluation [Internet]. [cited 2024 Oct 21]. Available from: https://www.healthdata.org/research-analysis/diseases-injuries-risks/factsheets/2021-diabetes-mellitus-type-1-level-4-disease

23. Donnor T, Sarkar S. Insulin- Pharmacology, Therapeutic Regimens and Principles of Intensive Insulin Therapy. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 Oct 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK278938/

24. Hirsch IB, Juneja R, Beals JM, Antalis CJ, Eugene E Wright J. The Evolution of Insulin and How it Informs Therapy and Treatment Choices. Endocr Rev. 2020 May 12;41(5):733.

25. M Komorniczak -talk- I intermediate long_acting png: AP MDderivative work: English: Insulin is categorized by how fast it works it the body, how soon it peaks and then how long it lasts. Notice how rapid acting insulins have a rapid rise and fall while longer acting insulin builds more slowly to a stable baseline before declining. [Internet]. 2010 [cited 2024 Oct 21]. Available from: https://commons.wikimedia.org/wiki/File:Insulin_short-intermediate-long_acting.svg

26. MSF study reveals global double standard in diabetes care | Doctors Without Borders - USA [Internet]. [cited 2024 Oct 21]. Available from: https://www.doctorswithoutborders.org/latest/msf-study-reveals-global-double-standard-diabetes-care

27. Barber MJ, Gotham D, Bygrave H, Cepuch C. Estimated Sustainable Cost-Based Prices for Diabetes Medicines. JAMA Netw Open. 2024 Mar 27;7(3):e243474.

28. Sarbacker GB, Urteaga EM. Adherence to Insulin Therapy. Diabetes Spectr. 2016 Aug 1;29(3):166–70.

29. WHO Model List of Essential Medicines - 23rd list, 2023 [Internet]. [cited 2024 Oct 28]. Available from: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02

30. Kramer CK, Retnakaran R, Zinman B. Insulin and insulin analogs as antidiabetic therapy: A perspective from clinical trials. Cell Metab. 2021 Apr;33(4):740–7.

31. Cobry E, McFann K, Messer L, Gage V, VanderWel B, Horton L, et al. Timing of meal insulin boluses to achieve optimal postprandial glycemic control in patients with type 1 diabetes. Diabetes Technol Ther. 2010 Mar;12(3):173–7.

32. Luijf YM, Bon AC van, Hoekstra JB, DeVries JH. Premeal Injection of Rapid-Acting Insulin Reduces Postprandial Glycemic Excursions in Type 1 Diabetes. Diabetes Care. 2010 Oct;33(10):2152.

33. Kennedy MSN, Masharani U. Pancreatic Hormones & Antidiabetic Drugs. In: Katzung BG, editor. Basic & Clinical Pharmacology [Internet]. 14th ed. New York, NY: McGraw-Hill Education; 2017 [cited 2024 Oct 21]. Available from: accessmedicine.mhmedical.com/content.aspx?aid=1148439639

34. Heinemann L. Variability of insulin absorption and insulin action. Diabetes Technol Ther. 2002;4(5):673–82.

35. Gradel AKJ, Porsgaard T, Lykkesfeldt J, Seested T, Gram-Nielsen S, Kristensen NR, et al. Factors Affecting the Absorption of Subcutaneously Administered Insulin: Effect on Variability. J Diabetes Res. 2018 Jul 4;2018:1205121.

36. FDA. 020563s115lbl.pdf [Internet]. Humalog [Internet]. 2008. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020563s115lbl.pdf

37. FDA. 020986s082lbl.pdf [Internet]. Novolog [Internet]. 2012. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020986s082lbl.pdf

38. FDA. 021629s015lbl.pdf [Internet]. Apidra [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021629s015lbl.pdf

39. Braak EWT, Woodworth JR, Cerimele B, Kurtz D. Injection Site Effects on the Pharmacolcinetics and Glucodynamics of Insulin Lispro and Regular Insulin.

40. Tupola S, Komulainen J, Jääskeläinen J, Sipilä I. Post-prandial insulin lispro vs. human regular insulin in prepubertal children with Type 1 diabetes mellitus. Diabet Med J Br Diabet Assoc. 2001 Aug;18(8):654–8.

41. International Diabetes Federation. IDF DIABETES ATLAS Ninth edition 2019 [Internet]. 2020. Available from: https://diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf

42. European Medicines Agency (EMA). Insulin lispro Sanofi, INN-insulin lispro [Internet]. European Medicines Agency (EMA); 2017. Available from: https://www.ema.europa.eu/en/documents/product-information/insulin-lispro-sanofi-epar-product-information_en.pdf

43. Insulin aspart Sanofi | European Medicines Agency (EMA) [Internet]. 2020 [cited 2024 Oct 29]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/insulin-aspart-sanofi

44. Apidra | European Medicines Agency (EMA) [Internet]. 2009 [cited 2024 Oct 29]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/apidra

45. Thota S, Akbar A. Insulin. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Oct 29]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK560688/

46. Your Health Care Team| ADA [Internet]. [cited 2024 Oct 30]. Available from: https://diabetes.org/health-wellness/diabetes-and-your-health/your-healthcare-team

47. MEDEVIS [Internet]. [cited 2024 Oct 21]. Available from: https://edl.who-healthtechnologies.org/?toggle=on&indication%5B%5D=Diabetes+mellitus

48. GRADE approach [Internet]. [cited 2024 Oct 29]. Available from: https://training.cochrane.org/grade-approach

49. Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A, et al. Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus. Cochrane Database Syst Rev. 2016 Jun 30;2016(6):CD012161.

50. Nørgaard K, Sukumar N, Rafnsson SB, Saravanan P. Efficacy and Safety of Rapid-Acting Insulin Analogs in Special Populations with Type 1 Diabetes or Gestational Diabetes: Systematic Review and Meta-Analysis. Diabetes Ther. 2018 Jun 1;9(3):891–917.

51. Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A, et al. Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2018 Dec 17;12(12):CD013228.

52. O'Neill SM, Kenny LC, Khashan AS, West HM, Smyth RM, Kearney PM. Different insulin types and regimens for pregnant women with pre-existing diabetes. Cochrane Database Syst Rev. 2017 Feb 3;2(2):CD011880.

53. Persson B, Swahn ML, Hjertberg R, Hanson U, Nord E, Nordlander E, et al. Insulin lispro therapy in pregnancies complicated by type 1 diabetes mellitus. Diabetes Res Clin Pract. 2002 Nov;58(2):115–21.

54. Mathiesen ER, Kinsley B, Amiel SA, Heller S, McCance D, Duran S, et al. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. Diabetes Care. 2007 Apr;30(4):771–6.

55. World Health Organization. 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 [Internet]. Geneva: World Health Organization; 2018 [cited 2024 Oct 21]. 68 p. Available from: https://iris.who.int/handle/10665/272433

56. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy [Internet]. [cited 2024 Oct 29]. Available from: https://www.who.int/publications/i/item/WHO-NMH-MND-13.2

57. Overview | Diabetes in pregnancy: management from preconception to the postnatal period | Guidance | NICE [Internet]. NICE; 2015 [cited 2024 Oct 30]. Available from: https://www.nice.org.uk/guidance/ng3

58. American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care. 2017 Jan 1;40(Supplement_1):S64–74.

59. ISPAD Clinical Practice Consensus Guidelines 2022 - International Society for Pediatric and Adolescent Diabetes [Internet]. [cited 2024 Oct 29]. Available from: https://www.ispad.org/page/ISPADGuidelines2022

60. Hall JA, Summers KA, Obenchain RL. Cost and Utilization Comparisons Among Propensity Score-Matched Insulin Lispro and Regular Insulin Users. J Manag Care Pharm. 2003 May;9(3):263–8.

61. Chen K, Chang EY, Summers KH, Obenchain RL, Yu-Isenberg KS, Sun P. Comparison of costs and utilization between users of insulin lispro versus users of regular insulin in a managed care setting. J Manag Care Pharm JMCP. 2005 Jun;11(5):376–82.

62. Davey P, Grainger D, MacMillan J, Rajan N, Aristides M, Dobson M. Economic Evaluation of Insulin Lispro versus Neutral (Regular) Insulin Therapy Using a Willingness—To—Pay Approach. PharmacoEconomics. 1998 Mar 1;13(3):347–58.

63. Kilburg AC J; Heinen Kammerer, T; Daniel, D; Rychlik, R. Modelling als Instrument der Hypothesengenerierung gesundheitsökonomischer Studien am Beispiel der antidiabetischen Behandlung mit Insulin lispro im Vergleich zur Normalinsulintherapie. Gesundheitsökonomie Qual. 2002 Apr 22;7(02):96–100.

64. Reviriego J, Gomis R, Marañés JP, Ricart W, Hudson P, Sacristán JA. Cost of severe hypoglycaemia in patients with type 1 diabetes in Spain and the cost-effectiveness of insulin lispro compared with regular human insulin in preventing severe hypoglycaemia. Int J Clin Pract. 2008 Jul 1;62(7):1026–32.

65. Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. Can Med Assoc J. 2009 Feb 17;180(4):400.

66. Lloyd A, Townsend C, Munro V, Twena N, Nielsen S, Holman A. Cost-effectiveness of insulin aspart compared to human insulin in pregnant women with type 1 diabetes in the UK. Curr Med Res Opin.

2009 Mar 1;25(3):599–605.

67. Pratoomsoot C, Smith HT, Kalsekar A, Boye KS, Arellano J, Valentine WJ. An estimation of the long-term clinical and economic benefits of insulin lispro in Type 1 diabetes in the UK. Diabet Med. 2009 Aug 1;26(8):803–14.

68. Pollock RF, Valentine WJ, Pilgaard T, Nishimura H. The cost effectiveness of rapid-acting insulin aspart compared with human insulin in type 2 diabetes patients: an analysis from the Japanese third-party payer perspective. J Med Econ. 2011 Jan 1;14(1):36–46.

69. Cazarim M, Rodrigues J, Cruz-Cazarim E, Ayres L, Pereira L. Cost-effectiveness of insulin analogs from the perspective of the Brazilian public health system. Braz J Pharm Sci. 2017 Nov 13;53.

70. Valentine WJ, Van Brunt K, Boye KS, Pollock RF. Treating Type 1 Diabetes Mellitus with a Rapid-Acting Analog Insulin Regimen vs. Regular Human Insulin in Germany: A Long-Term Cost-Effectiveness Evaluation. Appl Health Econ Health Policy. 2018 Jun 1;16(3):357–66.

71. Nosrati M, Ahmadi Fariman S, Saiyarsarai P, Nikfar S. Pharmacoeconomic evaluation of insulin aspart and glargine in type 1 and 2 diabetes mellitus in Iran. J Diabetes Metab Disord. 2023 Jun 1;22(1):817–25.

72. Ewen M, Joosse HJ, Beran D, Laing R. Insulin prices, availability and affordability in 13 low-income and middle-income countries. BMJ Glob Health. 2019 Jun 1;4(3):e001410.

73. Wineinger NE, Zhang Y, Topol EJ. Trends in Prices of Popular Brand-Name Prescription Drugs in the United States. JAMA Netw Open. 2019 May 31;2(5):e194791–e194791.

74. Saeed A, Lambojon K, Saeed H, Saleem Z, Anwer N, Aziz MM, et al. Access to Insulin Products in Pakistan: A National Scale Cross-Sectional Survey on Prices, Availability, and Affordability. Front Pharmacol [Internet]. 2022;13. Available from: https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2022.820621

75. Zarei L, Peymani P, Moradi N, Kheirandish M, Mirjalili M, Zare M. Affordability of Medication Therapy in Diabetic Patients: A Scenario-Based Assessment in Iran's Health System Context. Int J Health Policy Manag. 2022;11(4):443–52.

76. Bayat S, Perumal-Pillay VA, Suleman F. Availability and pricing of insulin and related diagnostics in South Africa. J Pharm Policy Pract. 2024 Dec 31;17(1):2372467.

77. Drugs@FDA: FDA-Approved Drugs [Internet]. [cited 2024 Oct 29]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

78. Medicines | European Medicines Agency (EMA) [Internet]. [cited 2024 Oct 29]. Available from: https://www.ema.europa.eu/en/medicines

79. Pharmaceuticals and Medical Devices Agency [Internet]. [cited 2024 Oct 29]. List of Approved Products. Available from: https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html

80. Search criteria - Drug Product Database online query [Internet]. [cited 2024 Oct 29]. Available from: https://health-products.canada.ca/dpd-bdpp/

81. Administration (TGA) TG. Australian Register of Therapeutic Goods (ARTG) | Therapeutic Goods Administration (TGA) [Internet]. Therapeutic Goods Administration (TGA); 2021 [cited 2024 Oct 29]. Available from: https://www.tga.gov.au/resources/artg

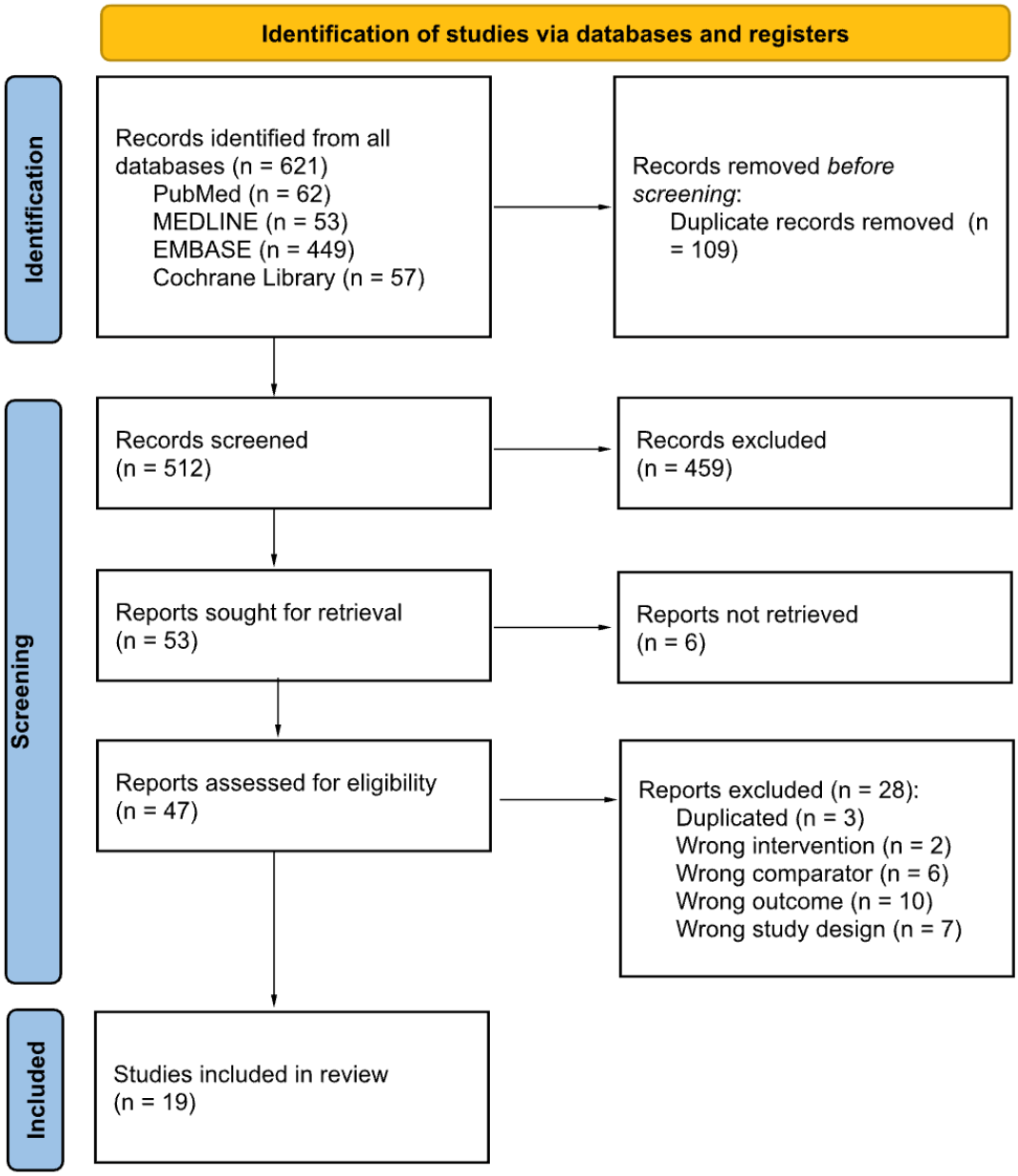
82. The International Pharmacopoeia [Internet]. [cited 2024 Oct 29]. Available from: https://digicollections.net/phint/2022/index.html#d/b.1

83. USP. USP Catalog [Internet]. 2024. Available from: https://static.usp.org/doc/referenceStandards/dailycatalog.pdf

84. CRS catalogue [Internet]. [cited 2024 Oct 29]. Available from: https://crs.edqm.eu/

85. Reference Standards catalogue search - 943 items - British Pharmacopoeia [Internet]. [cited 2024 Oct 29]. Available from: https://www.pharmacopoeia.com/shop/products/

## Annex 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.




From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

# Annex 2: Quality of evidence ratings of articles

As noted in Section 10.

**Table 18. Economic evidence profile: short-acting insulin analogs vs. regular human insulin in patients with diabetes mellitus**

Cost of insulin products

| Outcome / Study Design | Setting | Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Regular human insulin | Insulin analogs | Difference | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| Direct medical costs (per patient per month) 2 QES | US, patients with diabetes mellitus, 1998 - 1999 | No serious limitations | No serious inconsistency | No serious indirectness | No serious imprecision | Undetected | 519 USD | 543 USD (lispro) | +24 USD (*p* 0.5266) | ●●○○ Moderate (rated up for adjusting for confounders) |
| | US, patients with diabetes mellitus (no gestational diabetes), 2000 - 2001 | No serious limitations | No serious inconsistency | No serious indirectness | No serious imprecision | Undetected | - | - | -2,327 USD (*p* 0.072) | |

Cost-effectiveness of insulin products

| Outcome / Study Design | Setting | Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Main finding | Quality |
|---|---|---|---|---|---|---|---|---|
| Cost per QALY, 1 year time horizon 3 DAM, CEA | Germany, patients with T2DM | No serious limitations | Results differed by subpopulations (level of health care facility) | No serious indirectness | No serious imprecision | Undetected | Cost difference: 468 DM per year (insulin lispro cost-saving) | ●●○○ Moderate (rated down for inconsistency) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Brazil, patients with diabetes mellitus | No serious limitations | No serious inconsistency | No serious indirectness | No serious imprecision | Undetected | Insulin aspart: ICER 3,005.69 BRL<br>Insulin lispro: ICER 11,461.25 BRL | |
| Cost per QALY, 5-10 years time horizon<br>1 RCT, CEA | Japan, patients with T2DM | No serious limitations | No serious inconsistency | No serious indirectness | No serious imprecision | Undetected | Insulin aspart: dominant (cost-saving) | ●●●○<br>High |
| Cost per QALY, lifetime horizon<br>3 CEA | Canada, patients with T1DM and T2DM | No serious limitations | No serious inconsistency | No serious indirectness | No serious imprecision | Undetected | Insulin aspart:<br>-T1DM: dominant (cost-saving)<br>-T2DM: cost-effective (ICER 28,996 CAD)<br>Insulin lispro:<br>-T1DM: cost-effective (ICER 22,488 CAD)<br>-T2DM: not cost-effective (ICER 130,865 CAD) | ●●●○<br>High |
| | UK, patients with T1DM | No serious limitations | No serious inconsistency | No serious indirectness | No serious imprecision | Undetected | Insulin lispro: dominant (cost-saving) | |
| | Germany, patients with T1DM | No serious limitations | No serious inconsistency | No serious indirectness | No serious imprecision | Undetected | Insulin lispro: cost-effective (ICER 4,974€) | |
| Cost per life birth at term<br>1 DAM, CEA | UK, pregnant women with T1DM | No serious limitations | No serious inconsistency | No serious indirectness | No serious imprecision | Undetected | Insulin aspart: dominant (cost-saving) | ●●●○<br>High |
| Cost per severe hypoglycemia episode averted | Spain, patients with T1DM | No serious limitations | No serious inconsistency | Rates of hypoglycemia were obtained from a | No serious imprecision | Undetected | Cost to prevent 1 episode: 277 € | ●●○○<br>Moderate (rated down for indirectness) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 CEA | | | | different population | | | | |
| Incremental benefit per patient per year<br>1 CBA | Australia, patients with diabetes mellitus | No serious limitations | No serious inconsistency | No serious indirectness | No serious imprecision | Undetected | Average WTP: 39.31 AUD<br>Incremental benefit: 452.16 AUD (95% CI 574.08 – 330.24) | ●○○○<br>Low |
| Cost per 1% reduction in $Hb_{A1c}$ per patient per year<br>1 DAM, CEA | Iran, patients with T1DM and T2DM | No serious limitations | No serious inconsistency | Rates of hypoglycemia were obtained from a different population | No serious imprecision | Undetected | Insulin aspart:<br>-T1DM: cost-effective (ICER 83 USD)<br>-T2DM: NA | ●●○○<br>Moderate (rated down for indirectness) |
| CBA: cost-benefit analysis; CEA: cost-effectiveness analysis; DAM: decision-analytic model; QES: quasi-experimental study; RCT: randomized controlled trial; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus. | | | | | | | | |

# Annex 3: Letters of Support

Diabetes YOUTHCARE

REACHING YOUNG GHANAIANS LIVING WITH DIABETES

25th October 2024

Dear Members of the Expert Committee,

**RE: APPLICATION TO ADD RAPID-ACTING INSULIN ANALOGUES TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES**

I am writing on behalf of Diabetes Youth Care and as a Physician. I am currently the Executive Director of Diabetes Youth Care. Diabetes Youth Care (DYC) is an NGO and a support network for young people living with type 1 diabetes in Ghana. In the last 12 years we have been working to decrease the gap between our young warriors and medical personnel by increasing access of these young ones (T1D Warriors) to the medical community. One of our core responsibilities is to increase access to insulin and to make sure that these warriors have the right insulin at the right time. This is to reduce complications which are associated with type 1 diabetes mismanagement.

We whole heartedly support the inclusion of rapid-acting insulin analogues on the WHO EML. We have reviewed this important application and note the various responses and discussions around the issue over the years. We also recognize that there continue to be new and more expensive medications that are up for consideration to be included in the EML across a variety of indications. Long-acting analogues in 2021 were included in the EML and it is sad that resources have not been put forward to ensure that rapid-acting analogues are also included.

Rapid-acting insulins have been available for many years and are part of the status quo for treatment of type 1 diabetes in high-income countries. In countries like Ghana which is a mid- to lower income country, this type of insulin though present but not readily accessible to people living with diabetes due to the high cost and not being readily available across the whole country. Regular insulin works slower and does not allow for flexible dosing around varying amounts of carbohydrates and eating schedules. NPH and Premix insulins necessitates an additional injection daily and has an intense peak of action that puts people with diabetes at a higher risk of low blood sugar and makes them dependent on a rigid eating schedule. This is particularly difficult to achieve in some of the most remote and rural parts of the world like most of Ghana where regular access to food, medicine and healthcare is often an overwhelming challenge.

Analogue insulin allows for the more flexible diets and eating schedules, eating around faith events like Ramadan and Lent, lower risk and fear of hypoglycemia, and overall improved quality of life. It is an injustice that people in high-income countries have access to the most effective and health-promoting insulins available, while people in low- and middle-income

countries do not benefit from the same access. We believe that rapid-acting analogue insulin must be added to the WHO list of essential medicines.

As an organization which comprises of endocrinologists and other medical personnel to support these T1D warriors, we have recognized the benefits of the multiple dosing of insulin resulting in flexibility for them and allowing them to adjust and have better quality of life based on their needs at any particular time in their lives.

With this information and input from us, We hope that you would consider making rapid-acting insulin a part of the EML of WHO to help improve the lives of all people living with diabetes independent of where they live and their economic status. Insulin access is a human right and the right insulin is an even more basic human right.

Yours Sincerely

Nana Ama Barnes, MD
(Executive Director, DYC)

**Diabetes Youth Care**

**P O Box OS 2915, Osu,**

**Telephone: +233-503979411**

**Email: support@diabetesyouthcare.org**

Santé Diabète

**Stéphane Besançon, Executive Director of the NGO Santé Diabète and Associate Professor of Global Health at the Conservatoire National des Arts et Métiers**

October 25, 2024

Re: Application to add rapid-acting insulin analogues to the WHO Model List of Essential Medicines

Dear Members of the Expert Committee,

I am writing as the Executive Director of Santé Diabète, a non-governmental organization committed to improving diabetes care in Africa. Our twenty years of field experience in Mali, Burkina Faso, the Union of Comoros and France promoting better access to diabetes care and treatments lead us to support the inclusion of rapid-acting insulins in the Essential Medicines List (EML) of the World Health Organization.

Through our work, we have seen firsthand the stark contrast in access to diabetes care, particularly the availability of rapid-acting insulins, between countries. While rapid-acting insulins are commonly and easily accessible in France, they remain largely unavailable in Mali and other resource-limited settings in Africa.

This disparity leads to severe consequences for people living with diabetes in low and middle income countries, where insulin rationing, treatment protocols in need of updating, and a lack of access to essential diabetes care and education are common. rapid-acting insulins play a critical role in managing blood sugar levels, particularly around meals, and their absence puts patients at significant risk of life-threatening complications like diabetic ketoacidosis and chronic complications such as kidney failure or amputations. In France, where I have also worked extensively, rapid-acting insulins are part of a standard regimen, offering patients the flexibility and control they need to manage their condition effectively.

This situation in Mali, Burkina Faso and in the Union of the Comoros is unfortunately representative of many countries in Africa and the Indian Ocean, where economic barriers, supply chain challenges, and weak healthcare systems mean that access to even basic diabetes treatments is unreliable. Including rapid-acting insulins in the WHO Essential Medicines List (EML) would be an important step toward correcting these inequities. It would signal to governments, healthcare providers, and global health organizations the urgent need to prioritize insulin availability as part of diabetes care.

By incorporating rapid-acting insulins into the EML, the WHO would set the stage for improved procurement and affordability. This action would also encourage countries like Mali to

NGO Santé Diabète, Hippodrome Rue 254 Porte 69, Bamako, Mali
www.santediabete.org

strengthen their diabetes care systems, promoting better health outcomes and a more equitable approach to managing this chronic disease. My hope is that, with this inclusion, we can move toward a future where no one dies or suffers needlessly because of a lack of access to life-saving insulin, regardless of where they live.

Our organization, which has worked on the ground in Africa and in partnership with global diabetes communities, is eager to further support the WHO in its efforts to reduce health disparities. We believe that adding rapid-acting insulin to the EML would have a profound impact on the lives of millions of people across Africa and beyond.

Thank you for considering this crucial issue, and I remain at your disposal for any further information or support.

Sincerely,

Stéphane Besançon
Executive Director of NGO Santé Diabète and Associate Professor of Global Health at CNAM

NGO Santé Diabète, Hippodrome Rue 254 Porte 69, Bamako, Mali
www.santediabete.org

Charité | Charitéplatz 1 | 10117 Berlin | Germany

The Secretary
WHO Expert Committee on Selection and Use of Essential Medicines
Department of Health Products Policy and Standards
World Health Organization
20, Avenue Appia
1211 Geneva 27
Switzerland

INSTITUTE OF MEDICAL INFORMATICS

Prof. Dr. med. Dr. rer. nat. Felix Balzer
Chair

Postal address
Campus Charité Mitte
Charitéplatz 1 | 10117 Berlin

Visitor address
Invalidenstr. 90 | 10115 Berlin

T +49 30 450 570 425

Berlin, 27 October 2024

Written by:
Christoph Schippel
Assistant to Felix Balzer
T +49 30 450 570 425
F +49 30 450 755 1166
christoph.schippel@charite.de

**Re: Application to add short-acting insulin analogues to the WHO Model List of Essential Medicines**

Dear Members of the WHO Expert Committee,

As a pediatrician, diabetologist, and advocate for equitable access to specialized care for all people with diabetes, I am writing to express my strong support for the inclusion of short-acting insulin analogues on the WHO Model List of Essential Medicines. Ensuring the accessibility of these insulins is vital for diabetes management, particularly for people with diabetes living in low- and middle-income countries, where treatment options are often limited.

For the past three decades, short-acting insulin analogues, such as Eli Lilly's Humalog and Novo Nordisk's NovoRapid, have revolutionized diabetes care. These analogues offer more flexible and safer insulin regimens compared to human insulins like Actrapid, due to their faster onset and shorter duration of action. By mimicking natural insulin secretion more closely, they allow for more precise dosing around meals and for correcting high blood glucose levels, reducing the risks associated with under- or overdosing. This flexibility is crucial for people living with type 1 diabetes (T1D), as it accommodates individual physiological needs, varying lifestyles, gender and age-related differences, physical activity, and even religious practices such as fasting during Ramadan.

Short-acting insulin analogues are also essential for the use of advanced diabetes technologies such as insulin pumps, automated insulin delivery systems, sensor-augmented therapies and diabetes management apps. These technologies rely on the dynamics of fast-acting insulins in context of blood glucose or continuous glucose monitoring data. Without access to analogue insulins, individuals are unable to benefit from these technological advances, which have been shown to significantly improve glycemic outcomes, reduce the risk of hypoglycemia, and enhance overall quality of life and mental health.

The failure to include short-acting insulin analogues in the WHO EML, despite their demonstrated efficacy and the addition of long-acting analogues in 2021, is a significant oversight. Many people with diabetes in low and middle income countries continue to rely on older human insulins like NPH and regular insulin, which can only be used in rigid treatment schedules, do not reflect body physiology, and are associated with a higher risk of severe hypoglycemia and generally lower quality of life. This disparity exacerbates health inequities between high- and low-income settings.

As a clinician and living with type 1 diabetes myself, I witness firsthand the profound difference that access to insulin analogues makes in the lives of people with diabetes, particularly children and adolescents. The consequences of severe hypoglycemia, and fear of developing it, are significant contributors to diabetes distress, and reducing long-term risk by providing access to insulin analogues is crucial for physical health and emotional well-being alike.

It is unjust that people with diabetes in low and middle income countries are denied access to the same life-saving and quality-of-life-improving therapies that have become standard care in high income countries since decades. The WHO EML holds the potential to impact global health policy and encourage governments to make insulin analogues available to all people living with diabetes, regardless of their country of residence or economic status.

I urge the Expert Committee to consider not only the clinical efficacy of short-acting insulin analogues but also the profound impact they can have on the quality of life for people living with diabetes worldwide. By adding these insulins to the WHO EML, the WHO can take a significant step toward reducing health inequities and improving diabetes care globally.

Thank you for your attention to this important matter.

Sincerely,

PD Dr. med. Katarina Braune

Assistant Professior of Medical Informatics

Pediatrician, Diabetologist

**U.C.B. UNIVERSITE CATHOLIQUE DE BUKAVU, A.S.B.L.**

**Faculté de Médecine**

**Professeur Justin Cikomola Cirhuza**

October 25, 2024

Re: Application to add short-acting insulin analogues to the WHO Model List of Essential Medicines

Dear Members of the Expert Committee,

I am writing as an endocrinologist and a professor working in the Democratic republic of the Congo to support the inclusion of short-acting insulin analogues on the WHO EML. I have considered this important request. I have considered the evolution of the discussion on the issue over time. The addition of long-acting analogues in 2021, in my humble opinion, was an opportunity to mobilize resources to ensure the inclusion of short-acting analogues.

Short-acting insulins like Eli Lilly's Humalog and Novo Nordisk's Novorapid have been available for nearly 25-30 years and are part of the status quo for treatment of type 1 diabetes in high-income countries. Regular insulin works slower and does not allow for flexible dosing around varying amounts of carbohydrates and eating schedules. NPH necessitates an additional injection daily and has an intense peak of action that puts people with diabetes at a higher risk of low blood sugar and makes them dependent on a rigid eating schedule. This is particularly difficult to achieve in some of the most remote and rural parts of the world where regular access to medicine and healthcare is often an overwhelming challenge.

Analogue insulin allows for the use of insulin pump technology, more flexible diets and eating schedules, eating around faith events like Ramadan and others, lower risk and fear of hypoglycemia, and overall improved quality of life. It is an injustice that people in high-income countries can expect access to the most effective and health-promoting insulins available, while people in low- and middle-income countries do not benefit from the same access. I believe firmly that short-acting Analogue insulin must be added to the WHO list of essential medicines.

**Adresses**

- B.P. 285 BUKAVU (Rép. Dém. Congo)
- B.P. 02 CYANGUGU (Rwanda) 80
- B.P. 30 B-1348 Louvain-la-neuve (Belgique)
  Tél : +243 998088051
  Courriel : facmed@ucbukavu.cd

**Compte Bancaire**

Bruxelles : DBC Bank : N° 439-7951851-
Bukavu : BCDC : N° 170-0361774-

Swift : BCDCCDKI
BIAC : 33047176701-37

Risks related to taking human insulin include increased rates of hypoglycemia, which can be deadly. The use of human insulin puts a great burden onto patients, including their need for stricter management of time, loss of flexibility, and an increase in frequency and severity of low blood sugars. Fear of low blood glucose levels is one of the biggest indicators of diabetes distress and diabetes burnout. These costs in turn likely lead to demotivation, running blood glucose levels at a higher range to avoid more lows, and ultimately poorer health outcomes. Thus, while human insulin may be capable of providing acceptable long-term measures under optimal, controlled circumstances, it is not evident that it will achieve these outcomes for the individuals who have the least access to quality healthcare.

As a clinical patrician and based on my experience with patients, the 4+ doses of Lantus plus insulin aspart regimens that I routinely prescribe work best when considering the quality of life of patients. Thus, if I had the choice, I would not prescribe any of my patients NPH/regular therapy.

I hope that you will consider not only the data and clinical numbers related to the importance of short-acting analogue insulins, but also the quality of life of people with diabetes all around the world. Your choices and endorsements have profound impacts on how these individuals experience their day-to-day lives and can either compound or alleviate their struggles. I hope that the full weight of the WHO behind the importance of insulin analogues would facilitate bringing short-acting insulin to places where it can provide profound benefit to people living with T1D.

Sincerely,

Justin Cikomola Cirhuza

Justin Cikomola

Md, MMed (Internal Medicine, Endocrinology), Phd

Professor

Univesirté Catholique de Bukavu

**Adresses**

- B.P. 285 BUKAVU (Rép. Dém. Congo)
- B.P. 02 CYANGUGU (Rwanda) 80
- B.P. 30 B-1348 Louvain-la-neuve (Belgique)
  Tél : +243 998088051
  Courriel : facmed@ucbukavu.cd

**Compte Bancaire**

Bruxelles : DBC Bank : N° 439-7951851-
Bukavu : BCDC : N° 170-0361774-

Swift : BCDCCDKI
BIAC : 33047176701-37

Sonia Nabeta FOUNDATION

**October 25th, 2024**

Dear Members of the Expert Committee,

**Re: Application to add short-acting insulin analogues to the WHO Model List of Essential Medicines**

I am writing as a Consulting Physician the Sonia Nabeta Foundation (SNF) with experience in treating type 1 diabetes patients and as a person deeply concerned about global healthcare disparities to support the inclusion of short-acting insulin analogues on the WHO Essential Medicines List (EML). I have reviewed this important application and noted the various responses and discussions around the issue over the years. I also recognize that there continue to be new and expensive medications considered for inclusion in the EML across various indications. With the addition of long-acting analogues in 2021, it is imperative that resources are allocated to ensure short-acting analogues are also included.

Short-acting insulins like Eli Lilly's Humalog and Novo Nordisk's Novorapid have been available for nearly 25-30 years and are the standard treatment for type 1 diabetes in high-income countries. Regular insulin works slower and does not allow for flexible dosing around varying carbohydrate amounts and eating schedules. NPH necessitates an additional injection daily and has an intense peak of action that puts people with diabetes at higher risk of low blood sugar and makes them dependent on a rigid eating schedule. This is particularly challenging in remote and rural areas where access to medicine and healthcare is often limited.

Analogue insulin enables insulin pump technology, flexible diets and eating schedules, eating around faith events like Ramadan, lower risk and fear of hypoglycemia, improved quality of life. It is unjust that people in high-income countries have access to effective insulins while those in low- and middle-income countries do not. I firmly believe short-acting analogue insulin must be added to the WHO EML.

Risks associated with human insulin include increased hypoglycemia rates, which can be deadly. Human insulin imposes significant burdens on patients including stricter time management, loss of flexibility, increased frequency and severity of low blood sugars, fear of hypoglycemia, leading to diabetes distress and burnout. These consequences likely lead to demotivation, running blood glucose levels higher to avoid lows and poorer health outcomes.

As a general practitioner, I would not prescribe NPH/regular regimens if possible. Even with fewer doses, analogue insulin provides better outcomes. If it were equally effective in terms of overall management and

www.SoniaNabetaFoundation.org ♦ info@SoniaNabetaFoundation.org ♦ +256 786 034519

quality of life, the large diabetes communities in highly resourced counties would manage all patients with less invasive regimen.

I urge you to consider not only the clinical data but also the profound impact on quality of life for people with diabetes worldwide. Your endorsement has far-reaching consequences, affecting day-to-day experiences and alleviating struggles. The WHO's support for insulin analogues would facilitate access to short- acting insulin in areas where it can profoundly benefit those living with Type 1 Diabetes.

Thank you for considering this critical application.

Sincerely,

Dr. Gimono Martha

**Consulting Physician, Sonia Nabeta Foundation (SNF)**

www.SoniaNabetaFoundation.org ♦ info@SoniaNabetaFoundation.org ♦ +256 786 034519

# DiabetesIndia

The Research Trust of DiabetesIndia...

unite for diabetes



October 25, 2024

Re: Application to add rapid-acting insulin analogues to the WHO Model List of Essential Medicines

Dear Members of the Expert Committee,

We are writing this on behalf of Diabetes India [organization of Healthcare Professionals in Diabetes, website: www.diabetesindia.org.in] to support the inclusion of rapid-acting insulin analogues on the WHO EML. We have reviewed this important application and noted the various responses and discussions around the issue over the years. We also recognise that there continue to be new and expensive medications that are up for consideration to be included in the EML across various indications. With the addition of long-acting analogues in 2021, it is shocking that resources have not been put forward to ensure that short-acting analogues are also included.

Rapid-acting insulins like Eli Lilly's Humalog and Novo Nordisk's Novorapid have been available for nearly 25-30 years and are part of the status quo for the treatment of type 1 diabetes in high-income countries. Regular insulin works slower and does not allow for flexible dosing around varying amounts of carbohydrates and eating schedules. NPH necessitates an additional injection daily and has an intense peak of action that puts people with diabetes at a higher risk of hypoglycaemia and makes them dependent on a rigid eating schedule. This is particularly difficult to achieve in some of the most remote and rural parts of the world where regular access to medicine and healthcare is often an overwhelming challenge.

Analogue insulin is designed to mimic the body's natural insulin release pattern and physiology, improving glycaemic control, causing less glycaemic variability and reducing severe hypoglycaemic events. In addition, rapid-acting insulin is used in insulin pump therapy due to its aforementioned properties and overall improved quality of life. It is an injustice that people in high-income countries can expect access to the most effective and health-promoting insulins available, while people in low- and middle-income countries do not benefit from the same access. We believe firmly that short-acting Analogue insulin must be added to the WHO list of essential medicines.

**PAN No.:** AABTT3731C
**TAN No.:** MUMT13664A

**Head Office:**
50, Manoel Gonsalves Road, Bandra (West), Mumbai – 400 050. India
Ph.: +91-22-26557122 / 26429129 Fax: +91-22-56571637 Email: smsadikot@gmail.com

**All Correspondence to Secretariat:**

**Secretary General:**

**Dr. Banshi Saboo**
1 & 2 – Gandhi Park, Nr. Nehrunagar # Road, Ambawadi, Ahmedabad – 380 015. India
Ph.: +91-79-26304104 / 8104 Fax: +91-79-26302104 Email: banshisaboo@hotmail.com

**Dr. S. R. Aravind**
Diacon Hospital, 360 – 19th Main, 1st Block, Rajajinagar, Bengaluru – 560010. India
Ph.: +91-80-23323560/9909 Fax: +91-80-23325824 Email: draravind@hotmail.com

# DiabetesIndia

The Research Trust of DiabetesIndia...

unite for diabetes



Risks related to taking human insulin or premixed insulin include increased rates of hypoglycemia, which can be deadly. The use of human insulin puts a great burden on patients, including their need for stricter management of time, loss of flexibility, and an increase in frequency and severity of low blood sugars. Fear of low blood glucose levels is one of the biggest indicators of diabetes distress and diabetes burnout. These costs in turn likely lead to demotivation, running blood glucose levels at a higher range to avoid more lows, and ultimately poorer health outcomes. Thus, while human insulin may be capable of providing acceptable long-term measures under optimal, controlled circumstances, it is not evident that it will achieve these outcomes for the individuals who have the least access to quality healthcare.

As a Healthcare Professional involved in clinical practices in India, if I had the choice, I would not place any of my patients on NPH/regular regimens. Even though these regimens often involve only two doses a day of injected insulin compared to the 4+ doses of lantus plus insulin aspart that I routinely prescribe. If it were equally effective in terms of overall management and quality of life, surely we and the large diabetes communities in highly resourced countries would manage all our patients with this less invasive regimen.

We hope that you will consider not only the data and clinical numbers related to the importance of short-acting analogue insulins but also the quality of life of people with diabetes all around the world. Your choices and endorsements have profound impacts on how these individuals experience their day-to-day lives and can either compound or alleviate their struggles. We hope that the full weight of the WHO behind the importance of insulin analogues would facilitate bringing short-acting insulin to places where it can provide profound benefit to people living with T1D.

Sincerely,

Dr Banshi Saboo (Secretary Diabetes India)

Dr Amit Gupta (Joint Secretary Diabetes India)

**PAN No.:** AABTT3731C
**TAN No.:** MUMT13664A

**Head Office:**
50, Manoel Gonsalves Road, Bandra (West), Mumbai – 400 050. India
Ph.: +91-22-26557122 / 26429129 Fax: +91-22-56571637 Email: smsadikot@gmail.com

**All Correspondence to Secretariat:**

**Dr. Banshi Saboo**
1 & 2 – Gandhi Park, Nr. Nehrunagar # Road, Ambawadi, Ahmedabad – 380 015. India
Ph.: +91-79-26304104 / 8104 Fax: +91-79-26302104 Email: banshisaboo@hotmail.com

**Secretary General:**

**Dr. S. R. Aravind**
Diacon Hospital, 360 – 19th Main, 1st Block, Rajajinagar, Bengaluru – 560010. India
Ph.: +91-80-23323560/9909 Fax: +91-80-23325824 Email: draravind@hotmail.com

Sonia Nabeta FOUNDATION

October 25th, 2024

Dear Members of the Expert Committee,

**Re: Application to add rapid-acting insulin analogues to the WHO Model List of Essential Medicines**

I am Sroda Hottor the lead consulting physician for the Sonia Nabeta Foundation (SNF) type 1 diabetes (T1D) Clinic in Accra, Ghana within the West African Sub Region. Our clinic caters for the underserved population living with T1D in Ghana and neighboring countries. With a multidisciplinary team comprised of a pediatric endocrinologist, diabetes nurse, nutritionist and clinical psychologist; we provide free essential medical supplies including **INSULIN**, comprehensive medical care, ongoing support, self-management and education to children and adolescents with type 1 diabetes, 25yrs and under.

I write to strongly support the inclusion of rapid-acting insulin analogues on the WHO EML.
I have assessed this application and deem it relevant for rapid acting insulin analogues to be included in the WHO EML just as has been the addition of long-acting analogues in 2021.

In the management of T1D, long-acting analogues are paired with either short acting insulins or rapid acting analogues . Rapid acting insulin analogues provide a shorter period for onset of action and more importantly have a reduced risk of hypoglycemia which is even dear to those of us serving the paediatric population of diabetes. Rapid acting analogues have shown to give dosing flexibility and improved outcomes in Type1Diabetes management.

Basal bolus regimens with rapid-acting insulin gives our children more confidence in adherence and compliance as their fears of hypoglycemic incidence are alleviated. It also works well within our African context where our staple meals are heavy on carbohydrates as it affords dose flexibility with reduced fears of hypoglycemia. Rapid-acting insulin serves as the answer for managing children and adolescents in our part of the world where food insecurity serves as a barrier in T1D care. With children who have little to no access to meals and snacks and have one hefty meal each day; rapid-acting insulin provides the solution to their care whilst finding contextual sustainable solutions to meet their nutritional needs.

Clearly for these reasons and more that I extend my support to this cause. By enlisting of rapid-acting insulins on the WHO EML it will lead to it being readily available on our markets and facilitate competitive pricing

www.SoniaNabetaFoundation.org • info@SoniaNabetaFoundation.org • +256 786 034519

which increases affordability. It also will allow for the influx of insulin delivery technology such as insulin pumps in low socio-economic countries to allow our children have a better quality of life to grow and live out their dreams.

Sincerely,

Dr. Sroda Hottor

BSc BCHM, MBChB, MPH

**Consulting Pediatrician, Sonia Nabeta Foundation (SNF)**

www.SoniaNabetaFoundation.org • info@SoniaNabetaFoundation.org • +256 786 034519

**Department of Pediatrics**
**Ian M. Burr Division of**
**Pediatric Endocrinology and Diabetes**

**VANDERBILT UNIVERSITY**
**School of Medicine**

Cassandra N. Brady, MD
Karishma A. Datye, MD, MSCI
Justin M. Gregory, MD
Irene Hong-McAtee, MD
Sarah S. Jaser, PhD
Jennifer Kelley, MD, MSCE
Nidhi Gupta, MD

Yaa Kumah-Crystal, MD, MPH, MA
Jefferson P. Lomenick, MD
Daniel J. Moore, MD, PhD
Jennifer L. Najjar, MD
Jill H. Simmons, MD
William E. Russell, MD, Director
Ashley H. Shoemaker, MD, MSCI

Margaret S. Anderson, DNP, FNP-BC
Barbara Duffy, RN, MSN, CPNP
Cindy K. Lybarger, APRN, CDE
Ann M. Vander Woude, APRN, BC, CDE
Rachel M. Pasto-Crosby, RN, MSN, CPNP
Sara Duffus, MD
Daniel Tilden, MD – Clinical Fellow

October 22, 2024

Re: Application to add rapid-acting insulin analogues to the WHO Model List of Essential Medicines

Dear Members of the Expert Committee,

I am writing as a pediatric endocrinologist and as a person living with Type 1 diabetes for now nearly 50 years to support the inclusion of rapid-acting insulin analogues on the WHO EML. As I have previously been with consideration of long-acting insulin analogues, I remain perplexed, flummoxed, and appalled that rapid-acting insulin analogues and indeed all insulin analogues that have been widely available for more than 25 years have not already moved onto the EML.

I am surely grateful to the availability of the original animal insulins; they kept me alive to reach an age and stage where I can write these letters. I was thrilled in my later childhood when in the early 80's human insulin became available for the first time with its greater consistency. I will concede here at the outset that it is possible to manage diabetes with injected human insulin; it is possible to obtain a decent A1c on these regimens; it is unlikely that anyone is doing or will do a study to show an improvement in A1c across large numbers of individuals. At the same time, an A1c is an average of tens of thousands of little moments that go in to being a person living with T1D. And those moments are profoundly impacted by the type of insulin they are provided.

In living with diabetes treated with insulin, you quickly learn that kinetics dictates life. When your insulin reaches its maximum efficacy, you had better have food on board or you will risk a substantial low blood sugar. When you are on the original human insulins, this means planning out each day of your life around a strict schedule and food availability. If you are living in a situation where food access is uncertain or limited, the mix of NPH and regular is not the right insulin for you as these insulins force you to eat at specific times ***after*** taking them. This necessity distinguishes them from regimens built around long-acting insulin like glargine, detemir, and others that provide a level basal rate that demands little mandated food intake or timing and which were recently added to the EML. We are now discussing the critical next step which activates the true value of the long-acting analogues, which is the addition of faster acting analogues that stabilize this decision-making process and allow rapid treatment of food intake and hyperglycemia. The rapid-acting analogues can be taken at the time food is consumed, which lessens risk of food being unavailable; they also can be taken to decrease hyperglycemia over a short time frame. Finally, they enable the adoption of advanced insulin delivery

1500 21st Avenue South, Suite 1514 Nashville, TN 37212
Phone: 615.936.1874 Fax: 615.875.7633 www.pediatrics.mc.vanderbilt.edu

Department of Pediatrics
Ian M. Burr Division of
Pediatric Endocrinology and Diabetes

VANDERBILT UNIVERSITY
School of Medicine

technology, which surely will eventually be able to everyone if there is any compassion left in this world. In comparison, the risk of human insulins is borne out in the increased rates of hypoglycemia associated with taking them, which often results from timing mismatches between insulin intake and food availability. In addition, these low blood sugars, which can be life-threatening, likely enable the attainment of a "good" A1c (since A1c is an average) but at a clear cost to the patient. Indeed, the use of human insulin moves a great deal of costs onto the patient including their need for stricter management of time, loss of flexibility, and an increase in frequency and severity of low blood sugars and in so doing robs these patients of life and opportunity. These costs in turn may provide disincentives for individuals in these circumstances to be fully adherent with their diabetes regimen, given that they may not be able to afford going low in many circumstances, such as work, loss of access to food/shelter, or other life challenges. Thus, while human insulin is capable of providing acceptable long-term measures under optimal, controlled circumstances, it is not evident that it will achieve these outcomes for the individuals we are trying to serve. As far as I am aware, well-designed studies for outcomes and quality of life with combined rapid- and long-acting analogues vs human insulin have not been performed in low resource countries, which is the population we are addressing.

As a pediatric endocrinologist, I do not place any of my patients on NPH/regular regimens. Even though these regimens often involve only two doses a day of injected insulin compared to the 4+ doses of lantus plus insulin aspart that I routinely prescribe. If it were equally effective in terms of overall management and quality of life, surely I and the large diabetes communities in highly resourced countries would manage all our patients with this less invasive regimen. We of course do not do that as broad measures of 'equivalence' at population levels in terms of A1c do not portend equivalence for individuals or in their day-to-day lives or the quality of life they experience.

I hope that you will consider the impact of insulin therapy and selection on the lives of individuals with diabetes. Your choices and endorsements have profound impacts on how these individuals experience their day-to-day lives and can either compound or alleviate their struggles. They can either help them look to the future or confine them to the treatments and approaches of the past. I hope that the full weight of the WHO behind the importance of insulin analogues including inclusion of rapid-acting version would facilitate bringing insulin therapy to places where it can provide incredible, albeit immeasurable, benefit to persons living with T1D.

Sincerely,

Daniel J. Moore, MD, PhD
Director, Fellowship in Pediatric Endocrinology
Director, Pediatric Physician-Scientist Training Program
Faculty Leader, Edwards-Goodpasture MSTP College
Associate Professor of Pediatrics
Associate Professor of Pathology, Microbiology, and Immunology
Vanderbilt University Medical Center

1500 21st Avenue South, Suite 1514 Nashville, TN 37212
Phone: 615.936.1874 Fax: 615.875.7633 www.pediatrics.mc.vanderbilt.edu

**Letter Of Support: Rapid-Acting Insulin Analogue EML Application**

October 25, 2024

Re: Application to add rapid-acting insulin analogues to the WHO List of Essential Medicines

Dear Members of the Expert Committee,

I am writing to express my strong support for the inclusion of rapid-acting analogue insulin on the WHO's Essential Medicines List (EML). As a healthcare professional, researcher, advocate, diabetes educator, and a person who has lived with type 1 diabetes for 36 years, I have personally witnessed the significant impact that access to rapid-acting insulin can have on persons living with diabetes, especially type 1 diabetes. I firmly believe that its inclusion on the EML is key to improving global health outcomes, particularly for those living in low-and middle- income countries.

Rapid-acting analogue insulin like Eli Lilly's Humalog and Novo Nordisk's Novorapid have been available for nearly 3 decades. They are essential in the management of both type 1 diabetes and person's living with type 2 diabetes on insulin treatment. Its faster onset of action and shorter duration of action allow for better post meal glucose control and with a significantly reduced risk of hyperglycaemia in comparison to regular insulin which works slower and offers no flexibility with meals, increases risks of hypoglycaemic episodes. It will be more difficult for persons in Low-medium income countries to manage regular insulin, especially with the challenges of access to proper healthcare. Rapid-acting analogue insulin provides individuals with greater flexibility in meal timing, choice and varying quantities of meals, managing their daily routines, improving their quality of life and adherence to treatment protocols.

One of the most critical advantages of using rapid-acting insulin are it reduces the occurrence of hypoglycaemic episodes, particularly nocturnal hypoglycaemia, it allows for use in insulin pump technology, offers flexibility in meals and schedules, and eating around faith-based events like Ramadan. For many persons living with diabetes, including myself, this is a life-changing benefit, as hypoglycaemia not only impacts daily functioning but can also lead to serious health complication, including seizures, unconsciousness and even death. I believe strongly, that with all these advantages, people in low-middle income countries should be offered the same opportunity to benefit from this access to rapid-acting insulin as the high-income countries. As such, rapid-acting insulin analogues must be added to the list of WHO essential medicines.

The inclusion of rapid-acting insulin analogues aligns with the global health goals of reducing premature mortality from noncommunicable diseases (NCDs). However,

diabetes, particularly in underserved populations is a major contributor to the global NCD burden, and improving access to modern insulin like rapid-acting insulin analogues can significantly enhance the management of diabetes and prevent complications such as cardiovascular disease, kidney failure, and diabetic neuropathy.

While the upfront cost of rapid-acting insulin may be higher than the older forms (i.e., NPH/ regular insulin regimens), studies have shown that in the long run it is more cost effective. So, as a healthcare professional, I would rather place my patients on rapid-acting insulin analogues which would give them improved glycaemic control, reduced complications, better quality of life, and savings overtime (i.e., patients will be in better health and not spend money treating diabetes related complications).

In conclusion, the inclusion of rapid-acting analogue insulin on the WHO Essential Medicine List is an essential step needed to address the growing global diabetes epidemic. This analogue insulin has the potential to save lives, reduce diabetes related complications, and improve the overall quality of life for millions of persons living with diabetes globally. I respectfully urge the Expert Committee to consider the overwhelming evidence in favour of this rapid-acting analogue insulin and to recommend its addition to the EML.

Thank you in advance for your consideration.

Sincerely,

**Nkiruka Okoro, MD, MRes, MSc, BSc (Hons)**

**Senior Clinical Assistant, Cardiology (Heart Failure)**

**Queen Elizabeth University Hospital,**

**1345 Govan Road, Glasgow,**

**G51 4TF, Scotland.**

Diabet Centro

7 avenida, 9-64 zona 9
Edificio Zona Médica, Oficina 515
Ciudad de Guatemala, Guatemala
info@diabetcentro.com
Tels.: 2424-9412: 5410-5489

October 25, 2024

Re: Application to add rapid-acting insulin analogues to the WHO Model List of Essential Medicines

Dear Members of the Expert Committee,

As a diabetologist, diabetes professor and diabetes educator, I attend adults with diabetes in Guatemala City, Guatemala, Central America. I write in support of the petition to add rapid acting insulin analogues in the List of Essential Medicines, for the following reasons:

50% of people who receive clinical follow-up at this private diabetes clinic are on insulin. 5% of them are adults with type 1 diabetes on a basal-bolus regimen. Of the 95% of adults with type 2 diabetes who are on insulin, an additional 20% need rapid- acting insulin analogues to achieve glycemic control.

The lack of access to rapid -acting analogues in adults with type 2 diabetes has very important implications. First, glycemic variability (which is hard to achieve without prandial insulin in most cases) seriously affects the rate of progression and severity of microvascular complications, such as diabetic retinopathy, end stage renal disease and peripheral neuropathy, while these complications affect 30 - 35% of the adult population with diabetes.

Next, for people with diabetes and malnutrition, diabetic foot or other infections, the impossibility to use prandial insulin with their basal regimen slows the opportunities for nutritional improvement. The local diet is based on corn tortillas, beans, and plantains, all of which are high glycemic index carbohydrates. An 80% of the population has limited economic resources and is not able to sustain a low carb diet in order to avoid prandial insulin use while increasing food intake, improve nutritional status or achieve wound healing.

Another group in high need for rapid-acting analogues are people with diabetes who are on dialysis for chronic renal failure, because they are at high risk for hypoglycemia, and despite the fact that their A1c is lower than expected, 80% of patients on maintenance hemodialysis can present post- hemodialysis hyperglycemia. These patients will benefit greatly with an adequate use of rapid acting insulin analogues.

Of note, 61% of the population with diabetes who receive medical care at the Diabetcentro Clinic in Guatemala City are under 64y. 35% of them have some degree of retinopathy, and although the prevalence of vision- threatening diabetic retinopathy is higher on those over 64, cases of retinopathy in people under 64 are more severe. This may reflect a greater glycemic variability,

Diabet Centro

7 avenida, 9-64 zona 9
Edificio Zona Médica, Oficina 515
Ciudad de Guatemala, Guatemala
info@diabetcentro.com
Tels.: 2424-9412: 5410-5489

sustained over a longer period of time in this population. This fact points again towards the need for use of rapid-acting insulin analogues.

Other important issues to take into account when considering including rapid-acting insulin analogues in the EML list include the economic cost of insulin for people with diabetes. An insulin pen costs between USD. $27.00 - 70.51, plus $0.50 for each needle ($61.53 a month for needles, and a minimum estimate of $107.69 on insulin, for a person on a basal-bolus regimen). This makes insulin extremely expensive in a country where the minimum wage is US$448.72 a month. Only 22% of the Guatemalan population has social security, and fewer have access to private insurance.

About the cost of insulin syringes: Each insulin syringe with a 6mm needle costs $0.77 (20 cents more expensive than a pen needle per unit). Some governmental and non-profit organizations provide insulin users with 12 mm needles, which cause lipodystrophy and are related to a worse glycemic control. I kindly suggest you may consider including insulin injection supplies (needles, syringes, test strips and monitors, lancets) into the EML as well.

Plus, for the last two years Guatemala has suffered a scarcity of insulin supply: insulin pens are not available -except for the most expensive ones, even if people have to pay for them.

I understand rapid acting insulin analogues are more expensive than regular human insulin. But when you contemplate the benefits of a better glycemic control, less hypoglycemia and less glycemic variability, these benefits surpass the costs. While we continue educating about insulin and its proper use, decreasing costs and reasons to fear insulin related hypoglycemia will be of great help to improve diabetes management in Guatemala.

I respectfully urge you, as important decision makers and experts, who are aware of the above mentioned situations, to consider including rapid acting insulin analogues in the Essential Medication list, in benefit of all people with diabetes, especially in countries in most need, like the Latin American ones, like Guatemala.

Sincerely,
Fabiola Prado, MD, PhD
Director, Department of Diabetes Education
Instituto Diabetcentro
Guatemala City
Guatemala, Central America

Diabetes Care & Hormone Clinic

1-2, Gandhi Park, Near Nehrunagar Road
Ambawadi, Ahmedabad, - 380015. Gujarat, India
Call: 079 - 2630 41 04 / 2630 81 04

**Dr. Banshi Saboo**
M.D., Msc (Endo, UK), MNAMS (Diabetology), Ph.D., Dsc
Fellow - American College of Endocrinology (FACE)
FACP (USA), FICN (Canada), FRCP (UK)
Chair Elect : International Diabetes Federation (South)
East Asia Region)
Founder : Diabetes Care India (NGO)

**Dr. Vishal K. Vaidya**
Associate Diabetologist
+91 70450 16010

**Dr. Mehul Virani**
Associate Diabetologist
+91 85100 65577

**Dr. Tarjani Vyas**
Diabetologist
+91 99132 87370

**Dr. Jaina Khedawala**
Diabetologist
+91 97123 44694

**Dr. Amish Patel**
Diabetes Eye Specialist
+91 98980 83430

**Mrs. Smita Shah**
Obesity Consultant
+91 94263 75138

**Ms. Vaishnavi Raval**
Dietitian & Nutritionist
+91 99981 05077

**Dr. Swati Rathod**
**Dentist**
**+91 91045 18248**

Type - I Clinic

**Dr. Mahira Kadri**
Associate Consultant
+91 99983 93400

**Ms. Maitry Pancholi**
Diabetes educator
+91 91738 39648

**Mrs. Kinjal Chudasma**
Diabetes educator
+91 99985 23404

For prevention and reversal of diabetes

**Dr. Kumudi C**
Diabetologist
+91 81416 74812

October 25, 2024

Re: Application to add short-acting insulin analogues to the WHO Model List of Essential Medicines

Dear Members of the Expert Committee,

I am writing as a Chief Diabetologist at Diacare-Diabetes Care and Hormone clinic, Ahmedabad [involved in type 1 diabetes care and management for over 25 years] to support the inclusion of rapid-acting insulin analogues on the WHO EML. I have reviewed this important application and noted the various responses and discussions around the issue over the years. I also recognise that there continue to be new and expensive medications that are up for consideration to be included in the EML across various indications. With the addition of long-acting analogues in 2021, it is shocking that resources have not been put forward to ensure that short-acting analogues are also included.

Rapid-acting insulins like Eli Lilly's Humalog and Novo Nordisk's Novorapid have been available for nearly 25-30 years and are part of the status quo for treatment of type 1 diabetes in high-income countries. Regular insulin works slower and does not allow for flexible dosing around varying amounts of carbohydrates and eating schedules. NPH necessitates an additional injection daily and has an intense peak of action that puts people with diabetes at a higher risk of hypoglycaemia and makes them dependent on a rigid eating schedule. This is particularly difficult to achieve in some of the most remote and rural parts of the world where regular access to medicine and healthcare is often an overwhelming challenge.

Analogue insulin is designed to mimic the body's natural insulin release pattern and physiology, improving glycaemic control, causing less glycaemic variability and reducing severe hypoglycaemic events. In addition, rapid-acting insulin is used in insulin pump therapy due to is aforementioned properties and overall improved quality of life. It is an injustice that people in high-income countries can expect access to the most effective and health-promoting insulins available, while people in low- and middle-income countries do not benefit from the same access. I believe firmly that short-acting Analogue insulin must be added to the WHO list of essential medicines.

Diabetes Care & Hormone Clinic
1-2, Gandhi Park, Near Nehrunagar Road
Ambawadi, Ahmedabad, - 380015. Gujarat, India
Call: 079 - 2630 41 04 / 2630 81 04

**Dr. Banshi Saboo**
M.D., Msc (Endo, UK), MNAMS (Diabetology), Ph.D., Dsc
Fellow - American College of Endocrinology (FACE)
FACP (USA), FICN (Canada), FRCP (UK)
Chair Elect : International Diabetes Federation (South) East Asia Region)
Founder : Diabetes Care India (NGO)

**Dr. Vishal K. Vaidya**
Associate Diabetologist
+91 70450 16010

**Dr. Mehul Virani**
Associate Diabetologist
+91 85100 65577

**Dr. Tarjani Vyas**
Diabetologist
+91 99132 87370

**Dr. Jaina Khedawala**
Diabetologist
+91 97123 44694

**Dr. Amish Patel**
Diabetes Eye Specialist
+91 98980 83430

**Mrs. Smita Shah**
Obesity Consultant
+91 94263 75138

**Ms. Vaishnavi Raval**
Dietitian & Nutritionist
+91 99981 05077

**Dr. Swati Rathod**
**Dentist**
**+91 91045 18248**

Type - I Clinic

**Dr. Mahira Kadri**
Associate Consultant
+91 99983 93400

**Ms. Maitry Pancholi**
Diabetes educator
+91 91738 39648

**Mrs. Kinjal Chudasma**
Diabetes educator
+91 99985 23404

For prevention and reversal of diabetes

**Dr. Kumudi C**
Diabetologist
+91 81416 74812

Risks related to taking human insulin or premixed insulin include increased rates of hypoglycemia, which can be deadly. The use of human insulin puts a great burden onto patients, including their need for stricter management of time, loss of flexibility, and an increase in frequency and severity of low blood sugars. Fear of low blood glucose levels is one of the biggest indicators of diabetes distress and diabetes burnout. These costs in turn likely lead to demotivation, running blood glucose levels at a higher range to avoid more lows, and ultimately poorer health outcomes. Thus, while human insulin may be capable of providing acceptable long-term measures under optimal, controlled circumstances, it is not evident that it will achieve these outcomes for the individuals who have the least access to quality healthcare.

As a Healthcare Professional involved in clinical practice, if I had the choice, I would not place any of my patients on NPH/regular regimens. Even though these regimens often involve only two doses a day of injected insulin compared to the 4+ doses of lantus plus insulin aspart that I routinely prescribe. If it were equally effective in terms of overall management and quality of life, surely I and the large diabetes communities in highly resourced countries would manage all our patients with this less invasive regimen.

I hope that you will consider not only the data and clinical numbers related to the importance of short-acting analogue insulins, but also the quality of life of people with diabetes all around the world. Your choices and endorsements have profound impacts on how these individuals experience their day-to-day lives and can either compound or alleviate their struggles. I hope that the full weight of the WHO behind the importance of insulin analogues would facilitate bringing short-acting insulin to places where it can provide profound benefit to people living with T1D.

Sincerely,
Dr. Banshi Saboo
Chairman and Chief Diabetologist-Diacare
IDF Chair Elect-South-east Asia
Global Council Member-EASD


October 25, 2024

Re: Application to add rapid-acting insulin analogues to the WHO Model List of Essential Medicines

Dear Members of the Expert Committee,

I am a UK based family doctor with a specialist interest in diabetes. I am also co-founder of a charity called HelpMadina (www.helpmadina.org.uk). The charity is based in Sierra Leone, West Africa. One of the charity's projects includes the provision of diabetes care for patients with both Type 1 and Type 2 diabetes.

HelpMadina and T1International have been collaborating since 2010. We share a passion for improved diabetes care for all no matter where they live.

I am writing to support the inclusion of rapid-acting insulin analogues on the WHO EML. I have reviewed this important application and note the various responses and discussion around the issue over the years. I also recognize that there continue to be new and expensive medications that are up for consideration to be include in the EML across a variety of indications. With the addition of long-acting analogues in 2021, it is shocking that resources have not been put forward to ensure that rapid-acting analogues are also included.

rapid-acting insulins like Eli Lilly's Humalog and Novo Nordisk's Novorapid have been available for nearly 25-30 years and are part of the status quo for treatment of type 1 diabetes in high-income countries. Regular insulin works slower and does not allow for flexible dosing around varying amounts of carbohydrates and eating schedules. NPH necessitates an additional injection daily and has an intense peak of action that puts people with diabetes at a higher risk of low blood sugar and makes them dependent on a rigid eating schedule. This is particularly difficult to achieve in some of the most remote and rural parts of the world where regular access to medicine and healthcare is often an overwhelming challenge.

With regards to our patients with type 1 diabetes in Sierra Leone, having access to rapid-acting analogues has dramatically improved the health of our patients particularly the children and adolescents. They were underweight and stunted in growth because they were afraid to eat rice for fear of blood glucose spikes. Rice is the staple food in Sierra Leone. Having access to rapid-acting analogues has enabled us to introduce basal bolus regimes to incorporate the carbohydrate load of rice and our young patients are now gaining weight which is very encouraging.

Analogue insulin allows for the use of insulin pump technology, more flexible diets and eating schedules, eating around faith events like Ramadan and others, lower risk and fear of hypoglycemia, and overall improved quality of life. It is an injustice that people in high-income countries can expect access to the most effective and health-promoting insulins available, while people in low- and middle-income countries do not benefit from the same access. I believe firmly that rapid-acting Analogue insulin must be added to the WHO list of essential medicines.

Risks related to taking human insulin include increased rates of hypoglycemia, which can be deadly. The use of human insulin puts a great burden onto patients, including their need for stricter management of time, loss of flexibility, and an increase in frequency and severity of low blood sugars. Fear of low blood glucose levels is one of the biggest indicators of diabetes distress and diabetes burnout. These costs in turn likely lead to demotivation, running blood glucose levels at a higher range to avoid more lows, and ultimately poorer health outcomes. Thus, while human insulin may be capable of providing acceptable long-term measures under optimal, controlled circumstances, it is not evident that it will achieve these outcomes for the individuals who have the least access to quality healthcare.

As a doctor, if I had the choice, I would not place any of my patients on NPH/regular regimens. Even though these regimens often involve only two doses a day of injected insulin compared to the 4+ doses of lantus plus insulin aspart that I routinely prescribe. If it were equally effective in terms of overall management and quality of life, surely I and the large diabetes communities in highly resourced countries would manage all our patients with this less invasive regimen.

I hope that you will consider not only the data and clinical numbers related to the importance of rapid-acting analogue insulins, but also the quality of life of people with diabetes all around the world. Your choices and endorsements have profound impacts on how these individuals experience their day-to-day lives and can either compound or alleviate their struggles. I hope that the full weight of the WHO behind the importance of insulin analogues would facilitate bringing rapid-acting insulin to places where it can provide profound benefit to people living with T1D.

Sincerely

**Veronica Sawicki**

Dr Veronica Sawicki
MBBS London 1982
DRCOG
DTMH London 2021

**Letter of Support for Adding Short-Acting Insulin Analogues to the WHO Model List of Essential Medicines**

October 28, 2024

Re: Application to add short-acting insulin analogues to the WHO Model List of Essential Medicines

Dear Members of the Expert Committee,

Knowledge Ecology International (KEI), an organization with expertise in access to medicines, is writing in support of the application to include short-acting insulin analogues in the World Health Organization's Model List of Essential Medicines (EML). KEI has reviewed this application and we recognize that for people with type 1 diabetes in particular, access to these analogues is a matter of quality of life and safety.

For many decades, short-acting insulin analogues have been integral to diabetes care. Unlike older human insulin, these analogues provide precise glycemic control, support flexible dosing, and reduce the risk of hypoglycemia. The limitations of traditional human insulins place undue burdens on patients, particularly those in remote or underserved communities where access to consistent care and timely dosing can be more challenging. Regular insulin, while effective, has a slower onset, often requiring rigid dosing schedules that may not accommodate carrying daily needs.

In addition, short-acting insulin analogues allow for the use of advanced diabetes management technologies, such as pumps. This adaptability is also beneficial for patients, offering greater flexibility in food choices, exercise and lifestyle. Patients in high-income countries can routinely access these improved diabetes therapies, while those in low- and middle-income countries have restricted options or limited access altogether.

The addition of short-acting insulin analogues to the WHO EML would be an important step toward addressing these disparities in access. We urge the Expert Committee to consider not only the clinical data but also the meaningful improvements in quality of life and autonomy that insulin analogues afford to people with diabetes.

Sincerely,

*Arianna Schouten*

Arianna Schouten, MSc
*Senior Researcher*
*Knowledge Ecology International*

**Subject: Application to Include Rapid-Acting Insulin Analogues in the WHO Model List of Essential Medicines**

Dear Members of the Expert Committee,

I am writing as both a dedicated medical practitioner and a person living with type 1 diabetes for the past 19 years. My journey with this condition has deeply informed my understanding of the critical need for effective treatment options. I wholeheartedly support the inclusion of rapid-acting insulin analogues in the WHO Model List of Essential Medicines (EML). While the addition of long-acting analogues was a positive step, it is troubling that rapid-acting analogues have not yet been prioritised, especially given the complexities involved in managing type 1 diabetes.

According to the IDF Diabetes Atlas Report 2022, around 8.75 million people worldwide are living with type 1 diabetes. Alarmingly, one-fifth of these individuals (1.9 million) are in low- and middle-income countries, where access to effective treatment is even more critical. The time has come for us to advocate for the inclusion of rapid-acting insulin analogues in the EML, particularly for their specific need in managing hyperglycemia in a timely manner and their ability to be administered during or after meals, especially for individuals facing food rejection issues. As you would appreciate, almost all children face food rejection issues in younger years and it is incredibly difficult for parents to manage bolus with regular human insulin.

In my clinical experience, I have encountered many people with type 1 diabetes, including myself, who have faced significant difficulties with treating high blood sugar levels using regular human insulin. This can lead to unpredictable blood glucose levels and increased risks of hypoglycemia as well as prolonged hyperglycemia. In contrast, diabetes can be better managed with rapid-acting insulin, as individuals can inject to correct highs and administer insulin right before or after meals. This flexibility allows for adjustments in insulin doses based on carbohydrate intake, giving individuals greater control over their diabetes management.

While anecdotal evidence highlights these challenges, it is essential to focus on the lived experiences of those managing type 1 diabetes. The unpredictability of regular and NPH insulin often places individuals at a disadvantage, as the timing of insulin action can be out of their control. However, with rapid-acting insulin, the control largely remains in the hands of the person injecting the insulin, making it a critical factor in effective diabetes management.

Corresponding Address: Rawalpindi (Head office); 65-A, Street 3, Westridge-1, Opposite Rafay Mall, Peshawar Road.

Regional Offices:
Lahore | Karachi | Multan
www.meethizindagi.org

UAN: +92-300-034-1922
WhatsApp: +92-333-0194503

contact@meethizindagi.org
donations@meethizindagi.org
partnerships@meethizindagi.org

Research supports the need for rapid-acting insulin analogues. A systematic review and meta-analysis published in the Journal of Diabetes Research found that rapid-acting insulin analogues were associated with a lower number of total hypoglycemic episodes per month compared to regular human insulin. Specifically, the monthly rate of hypoglycemic episodes was 7% lower in the group using rapid-acting analogues (risk rate 0.93, 95% CI 0.87–0.99; 6180 individuals, 20 studies). This highlights the significant benefits of these insulins in reducing the risks of hypoglycemia.

The IDF Atlas also notes that 58% of type 1 diabetes cases are diagnosed in individuals aged 30 years or younger. These formative years should not be overshadowed by the challenges of managing a chronic illness. The burden of frequent low blood sugar episodes is not just a clinical concern; it takes an emotional toll, leading to diabetes distress and burnout. I've seen how this fear of hypoglycemia can rob people with type 1 diabetes of the joy in their daily lives, making them hesitant to engage fully in their personal and professional worlds.

As a practitioner, I would never consider prescribing NPH or regular insulin to those I support, knowing the significant risks they pose. Instead, I believe in empowering individuals with type 1 diabetes by providing them with the tools they need to manage their health with confidence and independence. Rapid-acting insulin analogues not only enhance glycemic control but also improve the overall quality of life, allowing individuals to live more freely without the constant constraints imposed by their condition.
I sincerely hope that you will consider not only the compelling data and clinical evidence supporting the necessity of rapid-acting insulin analogues but also the significant impact these treatments have on the daily lives of individuals with diabetes worldwide. Your decisions carry immense weight and can greatly influence the experiences of these individuals, either exacerbating their challenges or helping to alleviate them. It is my fervent wish that the WHO will champion the inclusion of insulin analogues, enabling access to rapid-acting insulins in regions where they can make a transformative difference for those living with type 1 diabetes.

Thank you for your consideration of this vital issue. Together, we can help ensure that all individuals with diabetes, regardless of where they live, have access to the most effective tools for managing their health.

Dr. Maham Tahir
CMH Lahore Medical and Dental College
Medical Officer, Bahria International Hospital Rawalpindi
Co-Lead, Fight for Five Campaign, TI International
Peer Leader, Meethi Zindagi