Insulin

Statut de médicament essentiel

Section: 18. Medicines for endocrine disorders > 18.5. Medicines for diabetes > 18.5.1. Insulins

EMLc | Codes ATC: A10AC01

Indication	Type 1 diabetes mellitus Code ICD11: 5A10
INN	Neutral insulin injection
Type de médicament	Biological agent
Type de liste	Liste de base (EML) (EMLc)
Additional notes	including quality-assured biosimilars
Formulations	Parenteral > General injections > SC: 40 IU per mL in 10 mL vial (soluble) ; 100 IU per mL in 10 mL vial (soluble) ; 100 IU per mL in 3 mL cartridge (soluble) ; 100 IU per mL in 3 mL pre-filled pen (soluble)
Historique des statuts LME	Ajouté pour la première fois en 1977 (TRS 615) Modifié en 1979 (TRS 641) Modifié en 1987 (TRS 770) Modifié en 1997 (TRS 882) Modifié en 2007 (TRS 950) Modifié en 2009 (TRS 958) Modifié en 2023 (TRS 1049)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.
Balises	Biological
Wikipédia	Insulin
DrugBank	Insulin (Insulin Human)

Recommandation du comité d'experts

The Expert Committee recognized insulin as a life-saving essential medicine for which a strong public health need existed and acknowledged that affordable and equitable access to insulin products continued to be a global health priority. The Committee was encouraged by the progress made by WHO through its prequalification programme to address this challenge with the prequalification of both human insulin and long-acting insulin analogue products in the recent past. The Committee recalled the recommendation in 2021 to include long-acting insulin analogues on the Model Lists in prefilled pen and cartridge delivery systems and considered that inclusion of human insulin in the same delivery systems would be consistent with that recommendation. The Committee considered that cartridges and prefilled pens may offer advantages for patients over vials and syringes in terms of ease of use, greater accuracy of dosing and improved adherence. The Expert Committee therefore recommended that the current listings for human insulin on the EML and EMLc be extended to include cartridge and prefilled pen delivery systems.

Contexte

Human insulin in vials has been available on the EML since 1977 and on the EMLc since 2007. In 2021, long-acting insulin analogues, in cartridge and prefilled pen delivery systems, were added to the Model Lists (1).

Pertinence pour la santé publique

Diabetes mellitus (type 1 and type 2) affected almost 460 million people worldwide in 2019, most of whom (about 95%) had type 2 diabetes (2). Proper management and treatment are crucial to prevent vascular complications and avoid adverse outcomes of hypoglycaemia. Insulin treatment is crucial for people with type 1 diabetes and for many with type 2 diabetes. It is typically administered through injections, with the preferred method being the basal bolus approach (3,4). This involves using intermediate or long-acting insulin once or twice a day and short-acting insulin three to five times a day before meals, adjusted based on factors such as blood glucose levels, growth, activity, illness and stress. Regular dose adjustments are necessary for effective diabetes management. The proper administration of insulin is essential for diabetes management. If the dose is too high, it can lead to hypoglycaemia, which may cause unconsciousness, seizures or death. If the dose is too low, glucose levels are poorly controlled, increasing the risk of diabetic ketoacidosis and long-term vascular complications, which can also result in morbidity and death if not treated appropriately. Reuse of needles for insulin administration is common in low-income countries and has been associated with infection (5).

Bénéfices

The application identified two systematic reviews that compared insulin cartridge or pen devices with vials and syringes. A 2016 systematic review and meta-analysis evaluated the efficacy of insulin pen devices compared with vial and syringe administration in patients with type 1 and type 2 diabetes (6). The review included 17 studies (10 retrospective cohort studies, six crossover randomized controlled trials and a parallel non-randomized clinical trial). Six of the 17 studies included people with type 1 diabetes. Data were reported for glycosylated haemoglobin (HbA1c) outcomes, hypoglycaemia, adherence (assessed using the medication possession ratio, which estimates the proportion of days the patient has medication available during the observation period), persistence (defined as the number of days until discontinuation of the medication), patient preference and quality of life. Meta-analyses were performed where possible. The following results were reported in the application. • For mean change in HbA1c at 12 months, there was very low-certainty evidence that cartridge/pen delivery systems improve HbA1c compared to vial and syringe administration (mean difference (MD) −0.28%, 95% CI −0.49% to −0.07%; four randomized controlled trials, 5079 participants). • For mean change in HbA1c at 12 months in insulin-naïve patients, there was low-certainty evidence that cartridge/pen delivery systems improve HbA1c compared to vial and syringe administration (MD −0.35%, 95% CI −0.50% to −0.19%; three randomized controlled trials, 2973 participants). • For percentage of patients with at least one episode of hypoglycaemia after 12 months, there was low-certainty evidence of fewer patients with hypoglycaemia with cartridge/pen delivery systems compared to vial and syringe administration (risk ratio (RR) 0.78, 95% CI 0.66 to 0.91; four randomized controlled trials, 7822 participants). • For mean change in medication possession ratio after 12 months, there was low-certainty evidence of improved adherence with cartridge/pen delivery systems compared with vial and syringe administration (MD 0.10, 95% CI 0.04 to 0.16; four randomized controlled trials, 6860 participants). • For percentage of persistent patients after 12 months, there was low-certainty evidence of more patients persistent at 12 months with cartridge/pen compared to vial and syringe administration (RR 1.31, 95% CI 1.15 to 1.48; six studies, 10 753 participants). The systematic review also reported a non-statistically significant trend favouring cartridge/pen delivery systems for the percentage of patients who achieved HbA1c < 7% (RR 1.12, 95% CI 0.99 to 1.27). Patient preference was measured in different studies using several non-validated questionnaires and different time horizons (7–11). These studies showed a tendency favouring cartridge/pen delivery systems. A single, small study used a short-form health survey (SF-36) to assess quality of life in 32 and 33 patients assigned to use cartridge/pen or vial and syringe administration, respectively (12). Cartridge/pen delivery systems were associated with statistically significant differences over vial and syringe administration in change from baseline scores for three sub-scales of the SF-36: physical component scores (+3.9 standard deviation (SD) 1.9 versus −1.0 SD 1.3, P = 0.037); physical role scores (+16.4 SD 9.4 versus −18.2 SD 8.4, P = 0.008); and general health status score (+9.8 SD 4.0 versus −2.5 SD 3.3, P = 0.021). Significant differences were not observed for the other sub-scales. A 2013 systematic review of 17 studies aimed to identify real-world factors affecting adherence to insulin therapy in patients with type 1 and 2 diabetes (13). Six studies used self-reported measures and 11 studies used calculated measures of adherence. Six of the studies reported adherence by delivery system: three in patients starting insulin therapy and three in patients switching from vial and syringe administration to a pen device. Five of these studies showed significantly higher adherence with a pen device than vial and syringe administration, measured using either medication possession ratio or proportion of days covered. The application pooled data from these studies and found low-certainty evidence of higher adherence with pen devices compared with vial and syringe administration (RR 1.16, 95% CI 1.12 to 1.21; six studies, 10 630 participants). Two recent studies conducted in North India (14)

and Lebanon (15) showed that patients preferred insulin pens/cartridges to vials and syringes for several reasons. Patients reported that the injections using pens/cartridges were less painful, more convenient and simpler, leading to fewer instances of missed insulin injections. Moreover, using pens/cartridges allowed patients to easily administer insulin for meals outside their homes or during vacations. Additionally, patients experienced less social stigma with the use of pens/cartridges compared with vials and syringes.

Torts

No data were presented in the application on harms associated with insulin administered using cartridge/pen delivery systems. The application stated that the alternate delivery method has been in use for more than 20 years in some countries and no harmful effects have been documented.

Rapport coût/efficacité

The cost of insulin pens/cartridges for diabetes management is higher than vials and syringes in most cases, particularly in low- and middle-income countries (17). However, when considering the total cost of diabetes care, claims data in the United States show cost savings with the use of pens/cartridges, primarily due to reduced hypoglycaemia compared to VaS (18,19). A retrospective observational study of individuals with type 2 diabetes enrolled in Medicaid in the United States, followed for 2 years, found significantly lower annualized health care costs in those people using pen therapy compared with those using syringes (US$ 14 857 versus US$ 31 765). This difference was mainly due to reduced hospital, diabetes-related and outpatient costs. However, prescription costs of syringes were significantly lower and prescription costs of pens significantly higher in patients who were switched from syringes to pens versus those who remained on syringes (18). A longitudinal, retrospective analysis of two claims' databases in the United States of individuals with type 1 or 2 diabetes who started insulin aspart therapy using pens (n = 10 577) or vials/syringes (n = 9305) found that vial/syringe use was associated with a 35% and 44% higher risk of hypoglycaemia compared with using pens/cartridges (19). Vial/syringe use was associated with 89% and 63% greater health care costs related to hypoglycaemic events compared with pen/cartridge use. A study on the price and availability of insulin in 13 low- and middle-income countries found that the median prices for short-acting, intermediate-acting and rapid-acting insulin and mixed human insulin were lower for vials than for pens/cartridges. For example, the median price for 10 mL of 100 IU/mL mixed human insulin was US$ 6.76 for vials, US$ 14.42 for cartridges and US$ 18.16 for pens (20). A cross-sectional survey evaluated price, availability and affordability of insulin products in eight cities in Pakistan (21). This study included a comparison of median prices and affordability of all types of insulin products combined (including originator and biosimilar products) in vial, pen and cartridge forms in the private sector. The median prices for 10 mL of 100 IU/mL insulin in vials, pens and cartridges were 735, 3070 and 1313 Pakistani rupees, respectively. The number of days' wages of the least-paid, unskilled public sector worker required to obtain a 30-day supply of human insulin in Pakistan was reported as 1.2 days for vials, 5.2 for pens and 2.2 for cartridges. In comparison, the number of days' wages for a 30-day supply of insulin was 3.3 days for vials and 6.9 for cartridges in Nepal, and 1.4 for vials, 5.1 for pens and 3.5 for cartridges in Bengaluru, India. In a survey in 2019 in leading diabetes centres in 37 low- and middle-income countries supported by the Life for a Child Program, 16.7% of people with diabetes younger than 25 years were using insulin pens. Additionally, 74% of respondents preferred insulin pens as their method of insulin delivery (5).

Directives de l'OMS

The 2018 WHO guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes include a strong recommendation for the use of human insulin to control blood glucose levels in adults with type 1 diabetes and in adults with type 2 diabetes for whom insulin is indicated, without reference to a particular delivery system (16).

Disponibilité

Human insulin in prefilled pens and cartridges have wide global regulatory approval. Current insulin prices and availability are a barrier to treatment in most low- and middle-income countries, and some subpopulations in higher-income countries cannot reliably access insulin because it is unavailable and/or unaffordable. To address this problem, in 2019 WHO issued a first invitation for expressions of interest for prequalification of human insulin. In 2022, a second invitation was issued (22). Products included in the second invitation included: • human insulin injection (soluble) 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial and cartridge; •

human intermediate-acting insulin 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial and cartridge (as compound insulin zinc suspension or isophane insulin); • long-acting insulin analogue solution for injection 100 U/mL vial and 100 U/mL in 3 mL cartridge. Human insulin solution 100 IU/mL and human insulin suspension 100 IU/mL in 10 mL vials and 3 mL cartridges manufactured by Novo Nordisk were prequalified by WHO in September 2022 (23).

Autres considérations

The technical team in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical team did not support the application highlighting the following reasons. • The body of evidence provided was insufficient and selective, with some systematic reviews on the topic omitted. • A substantial percentage of the included studies in the application were observational studies, with a risk of confounding bias. • No distinction was made between data on human and analogue insulin. • No adequate cost–effectiveness/utility/benefit analyses on the topic were provided. • Environmental impact concerns exist with plastic prefilled pens. • The evidence table provided was biased, with few data on people with type 1 diabetes, and the results on the advantages of human insulin were not reported.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2021 (including the 22nd WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1035; https://apps.who.int/iris/handle/10665/351172, accessed 6 October 2023).
2. Global Burden of Disease database [internet]. Washington, DC: Institute for Health Metrics and Evaluation; 2019 (https://vizhub. healthdata.org/gbd-results/, accessed 6 October 2023).
3. Type 1 diabetes in adults: diagnosis and management. London: National Institute for Health and Care Excellence; 2022 (NICE guid eline NG17; https://www.nice.org.uk/guidance/ng17, accessed 6 October 2023).
4. Danne T, Phillip M, Buckingham BA, Jarosz-Chobot P, Saboo B, Urakami T, et al. ISPAD Clinical Practice Consensus Guidelines 201 8: insulin treatment in children and adolescents with diabetes. Pediatr Diabetes. 2018;19(Suppl 27):115–35.
5. Klatman EL, Ogle GD. Access to insulin delivery devices and glycated haemoglobin in lower-income countries. World J Diabetes. 2 020;11(8):358–69.
6. Lasalvia P, Barahona-Correa JE, Romero-Alvernia DM, Gil-Tamayo S, Castaneda-Cardona C, Bayona JG, et al. Pen devices for insul in self-administration compared with needle and vial: systematic review of the literature and meta-analysis. J Diabetes Sci Technol. 2016;10(4):959–66.
7. Ahmann A, Szeinbach SL, Gill J, Traylor L, Garg SK. Comparing patient preferences and healthcare provider recommendations with the pen versus vial-and-syringe insulin delivery in patients with type 2 diabetes. Diabetes Technol Ther. 2014;16(2):76–83.
8. Coscelli C, Lostia S, Lunetta M, Nosari I, Coronel GA. Safety, efficacy, acceptability of a pre-filled insulin pen in diabetic patients ov er 60 years old. Diabetes Res Clin Pract. 1995;28(3):173–7.
9. Kadiri A, Chraibi A, Marouan F, Ababou MR, el Guermai N, Wadjinny A, et al. Comparison of NovoPen 3 and syringes/vials in the acc eptance of insulin therapy in NIDDM patients with secondary failure to oral hypoglycaemic agents. Diabetes Res Clin Pract. 1998;41 (1):15–23.
10. Seggelke SA, Hawkins RM, Gibbs J, Rasouli N, Wang CC, Draznin B. Effect of glargine insulin delivery method (pen device versus v ial/syringe) on glycemic control and patient preferences in patients with type 1 and type 2 diabetes. Endocr Pract. 2014;20(6):536– 9.
11. Shelmet J, Schwartz S, Cappleman J, Peterson G, Skovlund S, Lytzen L, et al. Preference and resource utilization in elderly patient s: InnoLet versus vial/syringe. Diabetes Res Clin Pract. 2004;63(1):27–35.
12. Lee IT, Liu HC, Liau YJ, Lee WJ, Huang CN, Sheu WH. Improvement in health-related quality of life, independent of fasting glucose concentration, via insulin pen device in diabetic patients. J Eval Clin Pract. 2009;15(4):699–703.
13. Davies MJ, Gagliardino JJ, Gray LJ, Khunti K, Mohan V, Hughes R. Real-world factors affecting adherence to insulin therapy in pat ients with type 1 or type 2 diabetes mellitus: a systematic review. Diabet Med. 2013;30(5):512–24.
14. Singh R, Samuel C, Jacob JJ. A comparison of insulin pen devices and disposable plastic syringes – simplicity, safety, convenience and cost differences. Eur Endocrinol. 2018;14(1):47–51.
15. Ramadan WH, Khreis NA, Kabbara WK. Simplicity, safety, and acceptability of insulin pen use versus the conventional vial/syring e device in patients with type 1 and type 2 diabetes mellitus in Lebanon. Patient Prefer Adherence. 2015;9:517–28.
16. Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults wi th diabetes mellitus. Geneva: World Health Organization; 2018 (https://iris.who.int/handle/10665/272433, accessed 6 October 20 23).
17. Ball D, Ewen M, Laing R, Beran D. Insulin price components: case studies in six low/middle-income countries. BMJ Glob Health. 20 19;4(5):e001705.
18. Pawaskar MD, Camacho FT, Anderson RT, Cobden D, Joshi AV, Balkrishnan R. Health care costs and medication adherence associ ated with initiation of insulin pen therapy in Medicaid-enrolled patients with type 2 diabetes: a retrospective database analysis. Clin Ther. 2007;29(6 Pt 1):1294–305.
19. Asche CV, Luo W, Aagren M. Differences in rates of hypoglycemia and health care costs in patients treated with insulin aspart in pens versus vials. Curr Med Res Opin. 2013;29(10):1287–96.
20. 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;4(3):e001410.
21. Saeed A, Lambojon K, Saeed H, Saleem Z, Anwer N, Aziz MM, et al. Access to insulin products in Pakistan: a national scale cross-se ctional survey on prices, availability, and affordability. Front Pharmacol. 2022;13:820621.
22. 2nd invitation to manufacturers of human insulin and insulin analogues to submit an Expression of Interest (EOI) for product eval uation to the WHO Prequalification Team --- Biotherapeutic Products (BTPs). Geneva: World Health Organization; 2022 (https://ex tranet.who.int/prequal/sites/default/files/document_files/EOI_Insulin_V2_May2022.pdf, accessed 6 October 2023).
23. Medicines (finished pharmaceutical products/biotherapeutic products) – Prequalification [internet]. Geneva: World Health Orga nization; (https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products, accessed 6 October 2023).