Insulin glargine

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

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

ATC codes: A10AE04

Indication	Type 1 diabetes mellitus ICD11 code: 5A10
INN	Insulin glargine
Medicine type	Biological agent
List type	Core
Formulations	Parenteral > General injections > SC: 100 units per mL
EML status history	Application rejected in 2017 (TRS 1006) Application rejected in 2019 (TRS 1021)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	insulin degludec (ATC codes: A10AE06) Parenteral > General injections > SC: 100 units per mL insulin detemir (ATC codes: A10AE05)
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Insulin glargine
DrugBank	Insulin glargine

Expert Committee recommendation

The Committee acknowledged that insulin is a life-saving essential medicine for which a compelling public health need exists. Yet despite being available for almost 100 years, achieving reliable, equitable and affordable access to insulin remains a public health challenge in many countries. The Committee did not recommend the addition of insulin analogues to the EML, reiterating the conclusion of the 2017 Committee, that although the available evidence for long-acting insulin analogues shows some efficacy advantages and reduced hypoglycaemia compared to human insulin, the price differential that exists between analogue and human insulin remains disproportionately high in most settings. The Committee remained concerned about the ongoing problems of access and affordability of insulin worldwide, despite human insulin not being patented. The Committee noted the long-standing domination of the insulin market by three manufacturers, limiting broader competition and slowing the entry of biosimilars to the market. Recognizing the complexities of these problems and the need for a wider understanding of the insulin market and access to insulin, the Committee recommended WHO coordinate a series of actions to address the issues of insulin access and affordability. In the absence of other coordinated actions, the Committee considered that the inclusion of insulin analogues for adults on the EML would be inadequate to address the underlying issues of poor access and affordability of insulins more generally. The Committee recommended that a WHO-led approach should be multi-factorial and multi-disciplinary and should include: ■ establishment of an independent WHO technical working group on access to insulin; ■ consultation with Member States and other stakeholders to identify/ clarify barriers to access at country level; ■ strategies to address current regulatory barriers for biosimilar insulins, such as the expansion of the WHO Prequalification Programme; ■ development of a comprehensive approach to address insulin prices, including mechanisms for pooled procurement; ■ identification of evidence and research gaps regarding insulin use and supply,

including setting-specific differences in clinical practice and health systems (e.g. food insecurity, displaced populations, emergencies). The Committee would welcome a report that comprehensively describes the actions that are undertaken by WHO over the next biennium and an application that reviews in-depth the current challenges for optimal global access and the role of insulin analogues in children.

Background

The application proposed the inclusion of long-acting insulin analogues (insulin detemir, insulin glargine, insulin degludec, including biosimilars) on the core list of the EML for treatment of patients with type 1 diabetes. Human insulin has been included on the EML since the first list in 1977 (1). In 1985, the WHO Expert Committee on the Selection and Use of Essential Medicines approved the inclusion of isophane neutral protamine Hagedorn (NPH) insulin (2). Since 1996, different insulin analogues, altered forms of human insulins, have been introduced on markets worldwide. In recent years, additional comparative evidence on biosimilars and reference medications in terms of efficacy and safety became available. In 2017, at the 21st meeting of the Expert Committee of the WHO EML, an application for the inclusion of long-acting analogues to the EML was rejected due to the limited magnitude of the benefits of analogues over human insulin in terms of reduced glycated haemoglobin and reduced hypoglycaemia as compared to the large difference in price between analogues and human insulin (3). Since that time, additional evidence has become available encompassing both effectiveness and increasing affordability of analogues.

Public health relevance

Diabetes mellitus has an increasing worldwide prevalence. If current trends continue, it is estimated that 642 adults will be living with diabetes by 2040 (4). The incidence of type 1 diabetes mellitus (T1DM) accounts for a small proportion of all diabetes (range: 5–10%) (5). All people living with type 1 diabetes have an absolute need for insulin for survival. Insulin is also required by a subset of patients with type 2 diabetes (6). Lack of access to affordable insulin is a problem globally and contributes to the complications of untreated or sub-optimally treated diabetes and premature deaths (7).

Benefits

The application presented the findings of a network meta-analysis (NMA) to evaluate the comparative effectiveness and safety of long- or intermediate-acting insulin versus biosimilar insulins in patients with T1DM, updating the results of a previous systematic review. The review compared basal regimens and categorizes treatments as per class of basal insulin (i.e. intermediate acting, long-acting and ultra-long-acting), and specific type of basal insulin, including insulin origin and insulin frequency. The analyses were adjusted for bolus regimen. Sixty-eight primary studies (8–75) (and 12 companion reports) involving 15 150 patients with average age ranging from 23 to 54 years were included. Sixty-two (91%) studies were randomized controlled trials (RCTs) and the majority had an unclear/high risk of bias on random sequence generation, allocation concealment, selective reporting, and 'other' bias (e.g. funding bias). Details of the included studies are available in Appendix File 1 of the application at: https://www.who.int/selection_medicines/committees/expert/22/applications/ s18.5_insulin-analogues.pdf?ua=1. Primary efficacy outcomes of the network meta-analysis were A1c and fasting plasma glucose. Secondary efficacy outcomes were mortality, any (total) vascular complication, microvascular complications, macrovascular complications and quality of life. A1c A basal insulin class NMA was conducted including 26 RCTs and 9241 patients and three treatment nodes (long-acting, intermediate-acting and ultra-longacting biosimilar). Long-acting insulin was statistically superior to intermediateacting insulin (mean difference MD −0.14, 95%CI −0.21 to −0.07). A specific type of insulin NMA was conducted on the A1c outcome including 34 RCTs and 11 894 patients and nine treatment nodes. Across the 36 treatment comparisons, the following 11 showed statistically significant results: – Intermediate-acting (human) insulin administered four times a day was inferior to intermediate-acting (animal and human) insulin administered twice a day (mean difference MD 0.31, 95% CI 0.05 to 0.57). – Intermediate-acting (human) insulin administered qid was inferior to intermediate-acting (human) insulin administered bid (MD 0.43, 95%CI 0.23 to 0.63). – Intermediate-acting (human) insulin administered qid was inferior to intermediate-acting (human) insulin administered once daily (od) (MD 0.32, 95%CI 0.10 to 0.53). – Long-acting (biosimilar) insulin administered od was superior to intermediate-acting (human) insulin administered qid (MD −0.46, 95%CI −0.67 to −0.24). – Long-acting (human) insulin administered bid was superior to intermediate-acting (human) insulin administered qid (MD −0.49, 95%CI −0.70 to −0.29). – Long-acting (human) insulin administered bid was superior to intermediate-acting (human) insulin administered od (MD −0.18, 95%CI −0.30 to −0.06). – Long-acting (human) insulin administered od was superior to intermediate-acting (animal and human) insulin administered bid (MD

−0.19, 95%CI −0.37 to −0.01). – Long-acting (human) insulin administered od was superior to intermediate-acting (animal) insulin administered bid (MD −1.27, 95%CI −2.54 to −0.01). – Long-acting (human) insulin administered od was superior to intermediate-acting (human) insulin administered qid (MD −0.50, 95%CI −0.69 to −0.31). – Long-acting (human) insulin administered od was superior to intermediate-acting (human) insulin administered od (MD −0.18, 95%CI −0.29 to −0.08). – Ultra-long-acting (biosimilar) insulin administered od was superior to intermediate-acting (human) insulin administered qid (MD −0.44, 95%CI −0.64 to −0.23). A sensitivity analysis to examine the impact of imputing missing standard deviations on the results resulted in the exclusion of seven trials. The pairwise treatment comparisons above were no longer statistically significant when the seven trials were excluded. When meta-regression analyses were conducted for follow-up duration, A1c level (mild: <8%, severe: ≥8%); proportion of women; duration of diabetes; and risk of bias associated with random sequence generation and allocation concealment, none of the results remained statistically significant. Statistically significant results were shown for meta-regression analyses on: – bolus type (rapid vs short): long-acting (human) insulin administered od was superior to intermediate-acting (animal) insulin administered bid (MD −1.27, 95%CI −2.54 to −0.001); – study design (parallel or crossover trials): long-acting (human) insulin administered bid was superior to intermediate-acting (animal) insulin administered bid (MD −1.27, 95%CI −2.53 to −0.0007); – baseline A1c: intermediate-acting (animal and human) insulin administered bid was superior to intermediate-acting (animal) insulin administered bid (MD −1.32, 95%CI −2.63 to −0.02); – age: long-acting (human) insulin administered bid, was superior to intermediate-acting (animal) insulin administered bid (MD −1.31, 95%CI −2.58 to −0.04) and long-acting (human) insulin administered od was superior to intermediate-acting (animal) insulin administered bid (MD −1.28, 95%CI −2.54 to −0.007). Fasting plasma glucose A basal insulin class NMA was conducted on the fasting plasma glucose outcome including 21 RCTs, 7685 patients, and three treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (MD −1.03, 95%CI −1.33 to −0.73) and ultra-long-acting insulin was superior to intermediate-acting insulin (MD −1.45, 95%CI −2.12 to −0.79). A specific type of insulin NMA was conducted on the fasting plasma glucose outcome including 28 RCTs, 9773 patients, and eight treatment nodes. Across the 28 treatment comparisons, the following nine showed statistically significant results: – Long-acting (biosimilar) insulin administered od was superior to intermediate-acting (human) insulin administered bid (MD −1.07, 95%CI −1.98 to −0.15). – Long-acting (human) insulin administered bid was superior to intermediate-acting (human) insulin administered bid (MD −0.82, 95%CI −1.21 to −0.43). – Long-acting (human) insulin administered od was superior to intermediate-acting (human) insulin administered bid (MD −1.26, 95%CI −1.66 to −0.85). – Long-acting (human) insulin administered od was superior to intermediate-acting (human) insulin administered od (MD −1.15, 95%CI −1.82 to −0.49). – Long-acting (human) insulin administered od was superior to long-acting (human) bid (MD −0.43, 95%CI −0.82 to −0.05). – Ultra-long-acting (biosimilar) insulin administered od was superior to intermediate-acting (human) insulin administered qid (MD −1.20, 95%CI −2.31 to −0.09). – Ultra-long-acting (biosimilar) insulin administered od was superior to intermediate-acting (human) bid (MD −1.55, 95%CI −2.24 to −0.87). – Ultra-long-acting (biosimilar) insulin administered od was superior to intermediate-acting (human) insulin administered od (MD −1.45, 95%CI −2.34 to −0.56). – Ultra-long-acting (biosimilar) insulin administered od was superior to long-acting (human) insulin administered bid (MD −0.73, 95%CI −1.38 to −0.08). Mortality A NMA was not possible for all-cause mortality for basal insulin classes. Two pairwise meta-analyses were possible for long-acting versus intermediate-acting insulin (four RCTs, 1682 patients), as well as ultra-long-acting versus long-acting insulin (two RCTs, 1540 patients). None of the results were statistically significant. A NMA was not possible for all-cause mortality for specific types of insulin. Three pairwise meta-analyses were possible comparing long-acting (human) insulin administered bid versus intermediate-acting (human) insulin administered bid (two RCTs, 653 patients), long-acting (human) insulin administered od versus long-acting (biosimilar) insulin administered od (two RCTs, 1093 patients) and long-acting (human) insulin administered od versus ultra-long-acting (biosimilar) insulin administered od (two RCTs, 1540 patients). None of the results were statistically significant. Any (total) vascular complication A basal insulin class NMA was conducted on any vascular complication, including 11 RCTs and 4709 patients. Across the three treatment comparisons, none were statistically significant. A specific type of insulin NMA was conducted on any vascular complication including 13 RCTs and 5589 patients. Across the 10 treatment comparisons, none were statistically significant. Microvascular complications A basal insulin class NMA was conducted to compare long-acting, intermediateacting and ultra-long acting insulins on microvascular complications including eight RCTs and 3131 patients. The transitivity assumption was upheld but inconsistency could not be assessed since there were no closed loops in the network meta-analysis diagram. Across the three treatment comparisons, none were statistically significant. A specific type of insulin NMA was conducted on microvascular complications including 10 RCTs and 4011 patients. Across the 10 treatment comparisons, none were statistically significant. Macrovascular complications For basal insulin classes, a NMA was not possible for macrovascular complications. Two pairwise meta-analyses were possible; long-acting insulin versus intermediate-acting insulin (three RCTs, 998 patients) and ultra-longacting biosimilar insulin versus long-acting

insulin (three RCTs, 2098 patients). The results of pairwise treatment comparisons were not statistically significant. For specific types of insulin, a NMA was not possible for macrovascular complications. Two pairwise meta-analyses were possible for long-acting (human) insulin administered bid versus intermediate-acting (human) insulin administered bid (four RCTs, 1258 patients) and long-acting (human) insulin administered od versus ultra-long-acting (biosimilar) od (two RCTs, 1540 patients). The results were not statistically significant. Quality of life A NMA or pairwise meta-analyses were not possible for health-related quality of life for basal insulin classes or specific types of insulin. One study including 517 patients reported total quality of life and long-acting (human) insulin administered od was not statistically significant compared with intermediateacting (human) insulin administered bid. The same study reported general quality of life and long-acting (human) insulin administered od was not statistically significant compared with intermediate-acting (human) insulin administered bid. With respect to basal insulin classes, similar results were observed when long-acting insulin was compared to intermediate-acting insulin.

Harms

Weight change A basal insulin class NMA was conducted including 16 RCTs, 6822 patients, and three treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (MD −0.70, 95%CI −1.07 to −0.33). A specific type of insulin NMA was conducted including 20 RCTs, 8335 patients, and seven treatment nodes. Across the 21 treatment comparisons, the following four showed statistically significant results: – Long-acting (human) insulin administered bid was superior to intermediate-acting (human) insulin administered bid (MD −0.85, 95%CI −1.24 to −0.46). – Long-acting (human) insulin administered bid was superior to intermediate-acting (human) insulin administered od (MD −1.18, 95%CI −2.13 to −0.24). – Long-acting (human) insulin administered bid was superior to long-acting (biosimilar) insulin administered od (MD −0.96, 95%CI −1.91 to −0.01). – Long-acting (human) insulin administered bid was superior to ultra-long-acting (biosimilar) insulin administered od (MD −0.69, 95%CI −1.32 to −0.06). All-cause hypoglycaemia (defined differently across RCTs) A basal insulin class NMA was conducted including 17 RCTs and 5949 patients. Across the three treatment comparisons, none were statistically significant. A specific type of insulin NMA was conducted including 22 RCTs and 6917 patients. Across the 21 treatment comparisons, none were statistically significant. Major or serious hypoglycaemia (defined differently across RCTs) A basal insulin class NMA was conducted including 19 RCTs, 7324 patients, and three treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (odds ratio OR 0.63, 95%CI 0.51 to 0.76). A specific type of insulin NMA was conducted including 25 RCTs and 9300 patients. Across the 21 treatment comparisons, the following four showed statistically significant results: – Long-acting (biosimilar) insulin administered od was superior to intermediate-acting (human) insulin administered bid (OR 0.48, 95%CI 0.24 to 0.97). – Long-acting (human) insulin administered bid was superior to intermediate-acting (human) insulin administered bid (OR 0.69, 95%CI 0.54 to 0.88). – Long-acting (human) insulin administered od was superior to intermediate-acting (human) insulin administered bid (OR 0.53, 95%CI 0.39 to 0.72). – Long-acting (human) insulin administered od was superior to intermediate-acting (human) insulin administered od (OR 0.60, 95%CI 0.42 to 0.86). Minor or mild hypoglycaemia For basal insulin classes, a NMA was not possible. One pairwise meta-analysis was possible for long-acting versus intermediate-acting insulin (eight RCTs, 2949 patients) and the results were not statistically significant. A specific type of insulin NMA was conducted including 11 RCTs and 3926 patients. Across the 15 treatment comparisons, none were statistically significant. Nocturnal hypoglycaemia (defined differently across RCTs) A basal insulin class NMA was conducted including 16 RCTs, 6669 patients, and three treatment nodes. Long-acting insulin was statistically superior to intermediate-acting insulin (OR 0.71, 95%CI 0.57 to 0.89) and ultra-long-acting biosimilar insulin was statistically superior to intermediate-acting insulin (OR 0.60, 95%CI 0.42 to 0.86). A specific type of insulin NMA was conducted including 19 RCTs and 7564 patients. Across the 15 treatment comparisons, the following two showed statistically significant results: – Intermediate-acting (human) insulin administered bid was inferior to ultra-long-acting (biosimilar) insulin administered od (OR 1.58, 95%CI 1.11 to 2.25). – Long-acting (human) insulin administered bid was superior to intermediate-acting (human) insulin administered bid (OR 0.59, 95%CI 0.44 to 0.79). Incident cancers For basal insulin classes, a NMA was not possible. One pairwise meta-analysis was possible for long-acting versus intermediate-acting insulin (three RCTs, 1651 patients) and the results were not statistically significant. For specific types of insulin, a NMA was not possible. One pairwise metaanalysis was possible (two RCTs and 1204 patients), which compared long-acting (human) insulin administered od versus intermediate-acting (human) insulin administered bid. The results were not statistically significant. Any (total) adverse events, serious adverse events, and dropouts due to adverse events For basal insulin classes, NMAs were conducted on any adverse events including 16 RCTs and 5367 patients, on serious adverse events including 20 RCTs and 6840 patients, and on withdrawals due to adverse events including 14 RCTs and 5440 patients. Across the three treatment comparisons in each NMA, none were statistically significant. For specific types of insulin, NMAs were conducted on any adverse events including 22 RCTs and 6830 patients, on serious adverse events

including 26 RCTs and 8989 patients, and on withdrawals due to adverse events including 21 RCTs and 7795 patients. Across the 15 treatment comparisons in each NMA, none were statistically significant.

Additional evidence

The current application does not include data on long-acting insulin analogue use in children. Long-acting insulin analogues have been investigated extensively in the paediatric age-group in low- and high-resource settings and were found to be safe and effective (76–80). They are approved in children from age two years (glargine and detemir) or one year (degludec) (81). Long-acting analogues have also been successfully used in infants and have shown positive effects on glucose control and on hypoglycaemia. However, the evidence is based on case reports (82, 83).

Cost / cost effectiveness

Ten cost-effectiveness analyses reported in three studies compared long-acting insulin detemir once a day with intermediate-acting insulin NPH once a day (72, 73, 75). Two studies (72, 75) found that detemir was less costly and more effective, while the third (73) showed that detemir was more costly but also more effective than NPH. Two cost-effectiveness analyses reported in a single study compared long-acting insulin detemir once a day with long-acting insulin glargine once a day (74). This study demonstrated that detemir is more costeffective than glargine. Finally, a single cost-effectiveness analysis in a single study compared ultra-long-acting biosimilar insulin degludec once a day with long-acting insulin glargine once a day (71). Degludec was shown to be the more cost-effective treatment in comparison to glargine.

WHO guidelines

The WHO 2018 Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus (84) make the following recommendations regarding the use of insulin: – Use human insulin (short-acting regular human insulin and intermediate-acting human insulin (NPH insulin)) to manage blood glucose in adults with type 1 diabetes and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low quality evidence). – Consider long-acting insulin analogues to manage blood glucose in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (weak recommendation, moderate quality evidence for severe hypoglycaemia). Recommendations from the 2018 WHO guidelines targeting type 1 diabetes were based on evidence from systematic reviews of randomized controlled trials (85–87). For patients with type 1 diabetes, the mean difference in HbA1c level between short-acting insulin analogues and regular human insulin was −0.15% (95%CI −0.20% to −0.10%) (low quality evidence). The difference in HbA1c level in patients treated with short-acting insulin analogues compared with those treated with regular human insulin was not considered clinically meaningful by the guidelines development group. Long-acting insulin analogues and human NPH insulin had similar effects on HbA1c level (moderate quality evidence). Long-acting insulin analogues reduced risk for severe hypoglycaemia, but only the reduction with detemir was statistically significant (moderate quality evidence). The guideline panel concluded that the relatively modest overall benefit from insulin analogues was outweighed by the large price difference between human insulin and insulin analogues. Thus, the panel considered use of long-acting detemir and glargine insulin analogues as alternatives to human insulin only in specific circumstances, such as unexplained and frequent severe hypoglycaemic events.

Availability

Three pharmaceutical companies are solely responsible for the supply of almost all insulin on markets worldwide. Despite being available for almost 100 years, achieving reliable, equitable and affordable access to insulin, human or analogue, remains a public health challenge in many countries (88). The Committee recognized the need for a wider understanding of the complexities of access to insulin and the current insulin market and recommended WHO to prioritize the coordination of a series of actions to address the issues of insulin access and affordability

Other considerations

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it did not support the application to add long-acting insulin analogues (including biosimilars) to the EML, nor was the application developed in consultation with the technical department. The review found long-acting insulin analogues to be superior to intermediate acting insulin with regard to major or serious hypoglycaemia, which may

represent an advantage particularly in settings where food security is not reliable. Glucagon, used in the management of severe hypoglycaemia, has very limited availability in many low-resource settings (89). Thus, the lower incidence of major or serious hypoglycaemia associated with the use of (ultra) long-acting insulin analogues may offer further advantages in such settings. The Committee acknowledged and noted the comments received in relation to this application from organizations and individuals expressing concern about the potential inclusion of insulin analogues on the Model List and associated consequences.

1. The selection of essential drugs. Report of a WHO Expert Committee, 1977 (WHO Technical Report Series No. 615). Geneva: World Health Organization; 1977. Available from https://apps.who.int/iris/bitstream/handle/10665/41272/WHO_TRS_615.pdf, accessed 30 October 2019.

2. The use of essential drugs. Second report of the WHO Expert Committee (WHO Technical Report Series No. 722). Geneva: World Health Organization; 1985. Available from https://apps.who.int/iris/bitstream/handle/10665/38831/WHO_TRS_722.pdf, accessed 30 October 2019.

3. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 1006). Geneva: World Health Organization; 2017. Available from https://apps.who.int/iris/bitstream/handle/10665/259481/9789241210157-eng.pdf, accessed 30 October 2019.

4. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40–50.

5. You WP, Henneberg M. Type 1 diabetes prevalence increasing globally and regionally: the role of natural selection and life expectancy at birth. BMJ Open Diabetes Res Care. 2016;4(1):e000161.

6. Basu S, Yudkin JS, Kehlenbrink S, Davies JI, Wild SH, Lipska KJ et al. Estimation of global insulin use for type 2 diabetes, 2018-30: a microsimulation analysis. Lancet Diabetes Endocrinol. 2019;7(1):25–33.

7. Global Report on Diabetes. Geneva, Switzerland: World Health Organization, 2016.

8. Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart. Diabet Med. 2006;23(8):879–86.

9. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med. 2008;25(4):442–9.

10. Birkeland KI, Home PD, Wendisch U, Ratner RE, Johansen T, Endahl LA et al. Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. Diabetes Care. 2011;34(3):661–5.

11. Birtwell AJ, Owens DR, Jones IR, Hayes TM, Beale DJ, el-Shaboury AH et al. Comparison of highly purified semi-synthetic insulin and highly purified porcine insulin in the treatment of type I diabetes: interim report of a multi-centre randomised single blind study. Diabete Metab. 1984;10(5):295–8.

12. Blevins TC, Dahl D, Rosenstock J, Ilag LL, Huster WJ, Zielonka JS et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus(R)) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. Diabetes Obes Metab. 2015;17(8):726–33.

13. Bode BW, Buse JB, Fisher M, Garg SK, Marre M, Merker L et al. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN((R)) Basal-Bolus Type 1): 2-year results of a randomized clinical trial. Diabet Med. 2013;30(11):1293–7.

14. Bolli GB, Songini M, Trovati M, Del Prato S, Ghirlanda G, Cordera R et al. Lower fasting blood glucose, glucose variability and nocturnal hypoglycaemia with glargine vs NPH basal insulin in subjects with Type 1 diabetes. Nutr Metab Cardiovasc Dis. 2009;19(8):571–9.

15. Chatterjee S, Jarvis-Kay J, Rengarajan T, Lawrence IG, McNally PG, Davies MJ. Glargine versus NPH insulin: efficacy in comparison with insulin aspart in a basal bolus regimen in type 1 diabetes--the glargine and aspart study (GLASS) a randomised cross-over study. Diabetes Res Clin Pract. 2007;77(2):215–22.

16. Crutchlow MF, Palcza JS, Mostoller KM, Mahon CD, Barbour AM, Marcos MC et al. Single-dose euglycaemic clamp studies demonstrating pharmacokinetic and pharmacodynamic similarity between MK-1293 insulin glargine and originator insulin glargine (Lantus) in subjects with type 1 diabetes and healthy subjects. Diabetes Obes Metab. 2018;20(2):400–8.

17. Danne T, Lupke K, Walte K, Von Schuetz W, Gall MA. Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes. Diabetes Care. 2003;26(11):3087–92.

18. Davies M, Sasaki T, Gross JL, Bantwal G, Ono Y, Nishida T et al. Comparison of insulin degludec with insulin detemir in type 1 diabetes: a 1-year treat-to-target trial. Diabetes Obes Metab. 2016;18(1):96–9.

19. De Leeuw I, Vague P, Selam JL, Skeie S, Lang H, Draeger E et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obes Metab. 2005;7(1):73–82.

20. Derosa G, Franzetti I, Querci F, Romano D, D'Angelo A, Maffioli P. Glucose-lowering effect and glycaemic variability of insulin glargine, insulin detemir and insulin lispro protamine in people with type 1 diabetes. Diabetes Obes Metab. 2015;17(6):554–9.

21. Eichner HL, Lauritano AA, Woertz LL, Selam JL, Gupta S, Charles MA. Cellular immune alterations associated with human insulin therapy. Diabetes Res. 1988;8(3):111–5.

22. Fulcher GR, Gilbert RE, Yue DK. Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. Intern Med J. 2005;35(9):536–42.

23. Hamann A, Matthaei S, Rosak C, Silvestre L. A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes. Diabetes Care. 2003;26(6):1738–44.

24. Heise T, Nosek L, Ronn BB, Endahl L, Heinemann L, Kapitza C et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1

diabetes. Diabetes. 2004;53(6):1614–20.

25. Heise T, Hovelmann U, Nosek L, Hermanski L, Bottcher SG, Haahr H. Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine. Expert Opin Drug Metab Toxicol. 2015;11(8):1193–201.

26. Heise T, Bain SC, Bracken RM, Zijlstra E, Nosek L, Stender-Petersen K et al. Similar risk of exerciserelated hypoglycaemia for insulin degludec to that for insulin glargine in patients with type 1 diabetes: a randomized cross-over trial. Diabetes Obes Metab. 2016;18(2):196–9.

27. Heise T, Norskov M, Nosek L, Kaplan K, Famulla S, Haahr HL. Insulin degludec: Lower day-to-day and within-day variability in pharmacodynamic response compared with insulin glargine 300 U/mL in type 1 diabetes. Diabetes Obes Metab. 2017;19(7):1032–9.

28. Heller S, Koenen C, Bode B. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. Clin Ther. 2009;31(10):2086–97.

29. Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. Diabetes Care. 2001;24(2):296–301.

30. Home P, Bartley P, Russell-Jones D, Hanaire-Broutin H, Heeg JE, Abrams P et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes Care. 2004;27(5):1081–7.

31. Home PD, Rosskamp R, Forjanic-Klapproth J, Dressler A. A randomized multicentre trial of insulin glargine compared with NPH insulin in people with type 1 diabetes. Diabetes Metab Res Rev. 2005;21(6):545–53.

32. Iga R, Uchino H, Kanazawa K, Usui S, Miyagi M, Kumashiro N et al. Glycemic Variability in Type 1 Diabetes Compared with Degludec and Glargine on the Morning Injection: An Open-label Randomized Controlled Trial. Diabetes Ther. 2017;8(4):783–92.

33. Ikushima I, Kaku K, Hirao K, Bardtrum L, Haahr H. Pharmacokinetic and pharmacodynamic properties of insulin degludec in Japanese patients with type 1 diabetes mellitus reflect similarities with Caucasian patients. J Diabetes Investig. 2016;7(2):270–5.

34. Kobayashi M, Iwamoto Y, Kaku K, Kawamori R, Tajima N. 48-week Randomized Multicenter Open-label Parallel Group Phase 3 Trial to Compare Insulin Detemir and NPH Insulin Efficacy and Safety in Subjects with Insulin Requiring Diabetes Mellitus in a Basal-bolus Regimen. Journal of the Japan Diabetes Society. 2007;50(9):649–63.

35. Koehler G, Heller S, Korsatko S, Roepstorff C, Rasmussen S, Haahr H et al. Insulin degludec is not associated with a delayed or diminished response to hypoglycaemia compared with insulin glargine in type 1 diabetes: a double-blind randomised crossover study. Diabetologia. 2014;57(1):40–9.

36. Kolendorf K, Ross GP, Pavlic-Renar I, Perriello G, Philotheou A, Jendle J et al. Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in Type 1 diabetes. Diabet Med. 2006;23(7):729–35.

37. Korsatko S, Deller S, Koehler G, Mader JK, Neubauer K, Adrian CL et al. A comparison of the steady-state pharmacokinetic and pharmacodynamic profiles of 100 and 200 U/mL formulations of ultra-long-acting insulin degludec. Clin Drug Investig. 2013;33(7):515–21.

38. Lane W, Bailey TS, Gerety G, Gumprecht J, Philis-Tsimikas A, Hansen CT et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA. 2017;318(1):33–44.

39. Larsen ML, Bjerrum P, Egstrup K. A comparison of semisynthetic human insulin and porcine insulin in the treatment of established diabetes. Dan Med Bull. 1984;31(3):243–4.

40. Le Floch JP, Levy M, Mosnier-Pudar H, Nobels F, Laroche S, Gonbert S et al. Comparison of onceversus twice-daily administration of insulin detemir, used with mealtime insulin aspart, in basalbolus therapy for type 1 diabetes: assessment of detemir administration in a progressive treatto-target trial (ADAPT). Diabetes Care. 2009;32(1):32–7.

41. Linnebjerg H, Lam EC, Zhang X, Seger ME, Coutant D, Chua L et al. Duration of action of two insulin glargine products, LY2963016 insulin glargine and Lantus insulin glargine, in subjects with type 1 diabetes mellitus. Diabetes Obes Metab. 2017;19(1):33–9.

42. Mathiesen ER, Hod M, Ivanisevic M, Duran Garcia S, Brondsted L, Jovanovic L et al. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. Diabetes Care. 2012;35(10):2012–7.

43. Mathieu C, Hollander P, Miranda-Palma B, Cooper J, Franek E, Russell-Jones D et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab. 2013;98(3):1154–62.

44. Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab. 2012;14(9):859–64.

45. Oswald GA, Yudkin JS. A within patient cross over trial of 4 insulin regimens in antibody-negative, C-peptide negative patients. Diabetes Res. 1987;4(2):85–9.

46. Pedersen C, Hoegholm A. A comparison of semisynthetic human NPH insulin and porcine NPH insulin in the treatment of insulin-dependent diabetes mellitus. Diabet Med. 1987;4(4):304–6.

47. Pesic M, Zivic S, Radenkovic S, Velojic M, Dimic D, Antic S. Comparison between basal insulin glargine and NPH insulin in patients with diabetes type 1 on conventional intensive insulin therapy. Vojnosanit Pregl. 2007;64(4):247–52.

48. Efficacy and safety of insulin detemir in type 1 diabetes. 2007. (ClinicalTrials.gov Identifier NCT00595374). Bethesda: U.S. National Library of Medicines; 2016. Available from www.clinicaltrials.gov/ct2/show/study/NCT00595374, accessed 29 September 2019.

49. Pieber TR, Eugene-Jolchine I, Derobert E. Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European Study Group of HOE 901 in type 1 diabetes. Diabetes Care. 2000;23(2):157–62.

50. Pieber TR, Draeger E, Kristensen A, Grill V. Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. Diabet Med. 2005;22(7):850–7.

51. Pieber TR, Treichel HC, Hompesch B, Philotheou A, Mordhorst L, Gall MA et al. Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. Diabet Med. 2007;24(6):635–42.

52. Porcellati F, Rossetti P, Pampanelli S, Fanelli CG, Torlone E, Scionti L et al. Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. Diabet Med. 2004;21(11):1213–20.

53. Segovia Portoles R, Ferrer-Garcia JC, Merino-Torres JF, Penalba MT, Albalat Galera R, Pinon-Selles F.

[Optimal timing of insulin detemir injection in patients with type 1 diabetes and poor metabolic control]. Endocrinol Nutr. 2010;57(4):140–6.

54. Radman M, Jurisic D, Ljutic D, Jerkovic R, Kovacic N, Hozo IS. Assessing glycemia in type 1 diabetic patients using a microdialysis system for continuous glucose monitoring. Ann Saudi Med. 2007;27(3):166–70.

55. Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes Care. 2000;23(11):1666–71.

56. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes Care. 2000;23(5):639–43.

57. Renard E, Dubois-Laforgue D, Guerci B, Variability Study G. Non-inferiority of insulin glargine versus insulin detemir on blood glucose variability in type 1 diabetes patients: a multicenter, randomized, crossover study. Diabetes Technol Ther. 2011;13(12):1213–8.

58. Richard JL, Rodier M, Cavalie G, Mirouze J, Monnier L. Human (recombinant DNA) and porcine NPH insulins are unequally effective in diabetic patients. A comparative study using continuous blood glucose monitoring. Acta Diabetol Lat. 1984;21(3):211–7.

59. Rosenstock J, Park G, Zimmerman J, Group. USIGHTDI. Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. Diabetes Care. 2000;23:1137–42.

60. Rossetti P, Pampanelli S, Fanelli C, Porcellati F, Costa E, Torlone E et al. Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime. Diabetes Care. 2003;26(5):1490–6.

61. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. Clin Ther. 2004;26(5):724–36.

62. Stades AM, Hoekstra JB, van den Tweel I, Erkelens DW, Holleman F. Additional lunchtime basal insulin during insulin lispro intensive therapy in a randomized, multicenter, crossover study in adults : a real-life design. Diabetes Care. 2002;25(4):712–7.

63. Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. Diabetes Technol Ther. 2004;6(5):579–88.

64. Tunbridge FK, Newens A, Home PD, Davis SN, Murphy M, Burrin JM et al. Double-blind crossover trial of isophane (NPH)- and lente-based insulin regimens. Diabetes Care. 1989;12(2):115–9.

65. Vague P, Selam JL, Skeie S, De Leeuw I, Elte JW, Haahr H et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes Care. 2003;26(3):590–6.

66. van Golen LW, Veltman DJ, RG IJ, Deijen JB, Heijboer AC, Barkhof F et al. Effects of insulin detemir and NPH insulin on body weight and appetite-regulating brain regions in human type 1 diabetes: a randomized controlled trial. PLoS One. 2014;9(4):e94483.

67. Vaughan K. An Open-Label, Randomized, Multi-center, Parallel-Group Clinical Trial Comparing the Efficacy and Safety of Mylan's Insulin Glargine with Lantus in Type 1 Diabetes Mellitus Patients. Amsterdam: European Medicines Agency/EU Clinical Trials Register; 2017. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-000747-32/results, accessed 29 September 2019.

68. Verma M, Hazra P, Iyer H, Arun A, Akundi S, Dixit MN et al. Basalog® is similar to Lantus® in producing glycemic control in patients with type 1 diabetes mellitus on multiple daily insulin regimens. Int J Diabetes Dev Ctries. 2011;31(1):26–31.

69. Witthaus E, Stewart J, Bradley C. Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with Type 1 diabetes. Diabet Med. 2001;18(8):619–25.

70. Zachariah S, Sheldon B, Shojaee-Moradie F, Jackson NC, Backhouse K, Johnsen S et al. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. Diabetes Care. 2011;34(7):1487–91.

71. Evans M, Wolden M, Gundgaard J, Chubb B, Christensen T. Cost-effectiveness of insulin degludec compared with insulin glargine in a basal-bolus regimen in patients with type 1 diabetes mellitus in the UK. J Med Econ. 2015;18(1):56–68.

72. Gschwend MH, Aagren M, Valentine WJ. Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries. J Med Econ. 2009;12(2):114–23.

73. Tunis SL, Minshall ME, Conner C, McCormick JI, Kapor J, Yale JF et al. Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modeling analysis. Curr Med Res Opin. 2009;25(5):1273–84.

74. Valentine WJ, Palmer AJ, Erny-Albrecht KM, Ray JA, Cobden D, Foos V et al. Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine, and NPH. Adv Ther. 2006;23(2):191–207.

75. Valentine WJ, Aagren M, Haglund M, Ericsson A, Gschwend MH. Evaluation of the long-term cost-effectiveness of insulin detemir compared with neutral protamine hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in Sweden. Scand J Public Health. 2011;39(1):79–87.

76. Karges B, Kapellen T, Neu A, Hofer SE, Rohrer T, Rosenbauer J et al. Long-acting insulin analogs and the risk of diabetic ketoacidosis in children and adolescents with type 1 diabetes: a prospective study of 10,682 patients from 271 institutions. Diabetes Care. 2010;33(5):1031–3.

77. Thalange N, Deeb L, Iotova V, Kawamura T, Klingensmith G, Philotheou A et al. Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2015;16(3):164–76.

78. Mona HM, Maha AM, Hend SM, Hanan NM. Effect of insulin glargine on glycemic control in adolescents with type 1-diabetes. Egyptian Pediatric Association Gazette. 2015;63(2):35–8.

79. Sharef SW, Ullah I, Al-Shidhani A, Al-Farsi T, Al-Yaarubi S. Switching to multiple daily insulin injections in children and adolescents with type 1 diabetes: revisiting benefits from oman. Oman Med J. 2015;30(2):83–9.

80. Biester T, Blaesig S, Remus K, Aschemeier B, Kordonouri O, Granhall C et al. Insulin degludec's ultralong pharmacokinetic properties observed in adults are retained in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2014;15(1):27–33.

81. Danne T, Phillip M, Buckingham BA, Jarosz-Chobot P, Saboo B, Urakami T et al. ISPAD Clinical Practice Consensus Guidelines 2018: Insulin treatment in children and adolescents with diabetes.

Pediatr Diabetes. 2018;19 Suppl 27:115–35.

82. Passanisi S, Timpanaro T, Lo Presti D, Mammi C, Caruso-Nicoletti M. Treatment of transient neonatal diabetes mellitus: insulin pump or insulin glargine? Our experience. Diabetes Technol Ther. 2014;16(12):880–4.

83. Park JH, Shin SY, Shim YJ, Choi JH, Kim HS. Multiple daily injection of insulin regimen for a 10-month-old infant with type 1 diabetes mellitus and diabetic ketoacidosis. Ann Pediatr Endocrinol Metab. 2016;21(2):96–8.

84. 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. Geneva: World Health Organization; 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/272433/9789241550284-eng.pdf?ua=1, accessed 29 September 2019.

85. Tricco AC, Ashoor HM, Antony J, Beyene J, Veroniki AA, Isaranuwatchai W et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ. 2014;349:g5459.

86. Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007(2):CD005613.

87. 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(6):CD012161.

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

89. Ogle GD, Middlehurst AC, Silink M. The IDF Life for a Child Program Index of diabetes care for children and youth. Pediatr Diabetes. 2016;17(5):374–84.