Consideration of diabetes medicines as part of the revisions to 2017 WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc)

1. ***Long-acting insulin analogues:*** *Insulin glargine; Insulin detemir*

2. ***Second-line therapies (to be used in combination with metformin) for treatment of type 2 diabetes in adults, adolescents and children:*** sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter-2 inhibitors, glucagon-like peptide-1 agonists, basal insulins, bolus insulins, and biphasic insulins, including analogues.

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

It is intended to communicate changes to the 2017 WHO Model List of Essential Medicines for adults (EML) and Model List of Essential Medicines for children (EMLc) to national counterparts involved in the evidence-based selection of medicines for inclusion in national essential medicines lists (NEMLs), lists of medicines for inclusion in reimbursement programs, and medicine formularies for use in primary, secondary and tertiary care.

This document does not replace the full report of the WHO Expert Committee, 2017 and this summary should be read in conjunction with the full report (WHO Technical Report Series, No. 1006; http://apps.who.int/iris/bitstream/10665/259481/1/9789241210157-eng.pdf?ua=1).

The revised lists of essential medicines (in English) are available as follows:

2017 WHO Model List of Essential Medicines for adults (EML)
http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1

2017 Model List of Essential Medicines for children (EMLc)
http://www.who.int/medicines/publications/essentialmedicines/6th_EMLc2017_FINAL_amendedAug2017.pdf?ua=1

18.5: Insulins and other medicines used for diabetes

1. Rejected application for addition of long-acting insulin analogues to EML and EMLc

Insulin glargine (ATC Code: A10AE0); Insulin detemir (ATC Code : A10AE05)

Background

Lack of access to affordable insulin is a global problem: more than half of the people who need insulin are unable to afford or access it, which leads to health complications and early death (1, 2).

Long-acting insulin analogues are licensed globally for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above. Patent protection of these analogues is expiring, or will soon expire, in USA, Europe and elsewhere, and there is increasing interest in the potential of basal or long-acting biosimilar insulins.

In 2014, the European Medicines Agency approved Abasaglar® as a biosimilar of the reference medicine insulin glargine. In 2015 Basaglar® was approved by the FDA as a follow-on biological of insulin glargine treatment. Copies of the long-acting insulin glargine have been approved and introduced into the market in several countries, including China, India, Kenya, Mexico and Pakistan.

Application

The application proposed the addition of long-acting insulin analogues as a pharmacological class to the core list of the EML and EMLc for treatment of type 1 diabetes in adults, adolescents and children aged 2 years and above. As there is more evidence for its effectiveness and safety, it was proposed that insulin glargine be listed with a square box as representative of the class, with alternatives limited to insulin detemir and biosimilar insulin glargine.

Scientific evidence of benefits and harms

Insulins are hypoglycaemia-inducing agents. There is evidence that hypoglycaemia may adversely affect the cardiovascular risk profile, particularly in older people and in patients affected by diabetes of longer duration (3). Overall, published trials show that severe hypoglycaemia may increase cardiovascular mortality (4, 5). Preventing hypoglycaemia is as least as important for disease management and long-term prognosis as tight glycaemic control.

Evidence for safety was based on the systematic review and network meta-analysis (6). Significantly fewer episodes of severe hypoglycaemia were experienced by patients receiving detemir once or twice daily compared with those given NPH once or twice daily (odds ratio (OR) 0.62; 95% CI 0.42–0.91). In one RCT, glargine once daily was associated with a statistically significant increase in episodes of severe hypoglycaemia compared with detemir once or twice daily (OR 4.30; 95% CI 1.19–15.53). In the network meta-analysis, however, these findings were no longer statistically significant.

Other considerations

Long-acting insulin appeared to be more expensive than intermediate-acting insulin; however, the application reported instances of long-acting insulin being the cheaper of the two. Most importantly, if the price of long-acting insulins were to fall, the probability that they will be cost effective compared with NPH may increase (7). When biosimilar erythropoietins were approved, the price declined by 20% in a relatively short period of time (3 years) (8); other studies report a total decline of 30–40% (9). Biosimilar insulins have the potential to reduce treatment costs and thus improve access for patients, physicians and health-care systems.

WHO Guidelines

WHO guidelines on hypoglycaemic agents, including insulin analogues, are currently being developed.

Expert Committee recommendations

The Expert Committee noted that long-acting insulin analogues have been shown to be an effective treatment for type 1 diabetes in children, young people and adults.

However, the Committee noted that the magnitude of the benefit provided, compared with human insulin, was not large. The Committee considered that the benefits of insulin analogues over human insulin in terms of reduced glycated haemoglobin and reduced hypoglycaemia are modest and do not justify the current large difference in price between analogues and human insulin.

On the basis of this evaluation, **the Expert Committee did not recommend the addition of long-acting insulin analogues as a pharmacological class to the core list of EML and EMLc for treatment of type 1 diabetes in adults, adolescents and children aged 2 years and above.**

References

1. Global report on diabetes. Geneva, Switzerland: World Health Organization; 2016.
2. Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS): research findings [website]. Amsterdam: Health Action International (http://haiweb.org/what-we-do/acciss/research-findings/, accessed 3 March 2017).
3. Mannucci E, Monami M, Lamanna C, Gori F, Marchionni N. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis. 2009;19(9):604–12.
4. Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C et al. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367(12):1108–18.
5. Seaquist ER, Miller ME, Bonds DE, Feinglos M, Goff DC Jr, Peterson K et al. The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. Diabetes Care. 2012;35(2):409–14.

6. Tricco AC, Ashoor HM, Soobiah C, Hemmelgarn B, Moher D, Hutton B et al. Safety, effectiveness, and cost of long-acting versus intermediate-acting insulin for type 1 diabetes: protocol for a systematic review and network meta-analysis. Syst Rev. 2013;2:73.

7. Mulcahy AW, Predmore Z, Mattke S. The cost savings potential of biosimilar drugs in the United States. Santa Monica, CA: Rand Corporation; 2014.

8. Farfan-Portet MI, Gerkens S, Lepage-Nefkens I, Vinck I, Hulstaert F. Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures? Eur J Health Econ. 2014;15(3):223–8.

9. Muller R, Renner C, Gabay C, Cassata G, Lohri A, Hasler P. The advent of biosimilars: challenges and risks. Swiss Med Wkly. 2014;144:w13980.

2. *Comprehensive review of treatments for type 2 diabetes - rejected application for addition of second-line treatments for type 2 diabetes to EML and EMLc*

Background

In 2013, the Expert Committee evaluated evidence comparing four groups of oral hypoglycaemics against metformin (biguanide) and sulfonylureas *(1)*:

- dipeptidyl peptidase-4 (DPP-4) inhibitors
- thiazolidinediones (TZDs)
- alpha-glucosidase inhibitors, such as acarbose
- meglitinides.

The results from the 2013 review indicated that there were no apparent differences in efficacy across drug classes, and that sulfonylureas were the most cost-effective treatment option. Based on these analyses, the Expert Committee recommended that "there was insufficient evidence to show that any of the medicines in the four groups (DPP-4 inhibitors, alpha-glucosidase inhibitors, meglitinides, or thiazolidinediones) offered any efficacy or safety advantages over the existing medicines [i.e. metformin first-line and sulfonylurea second-line] included in the EML".

Since then, a new drug class has entered the market in several countries for the treatment of patients with type 2 diabetes (T2D) — sodium-glucose cotransporter-2 (SGLT-2) inhibitors. In addition, a fourth DPP-4 inhibitor (alogliptin) and a third glucagon-like peptide 1 (GLP-1) agonist (dulaglutide) have appeared, and new data have been published on the impact on cardiovascular outcomes of some of the new drugs (e.g. GLP-1 agonists, DDP-4 inhibitors and SGLT-2 inhibitors).

Given the newer agents recently approved in most countries and additional evidence from randomized controlled trial (RCTs) published over the past 5 years for the existing and newer agents, there is a need to revisit comparative efficacy, safety and cost.

The comparative assessment in the application was based on an update of a previous CADTH (Canadian Agency for Drugs and Technologies in Health) systematic review and network meta-analyses of second-line therapies for T2D (*2*). In addition, the application reviewed pharmacological treatments for patients with T2D who are at high risk for cardiovascular events. Third-line therapies were not assessed.

Application

The application proposed updating of section 18.5 Insulins and other medicines used for diabetes of the EML and EMLc with a comprehensive and comparative assessment of all available second-line therapies (to be used in combination with metformin) for treatment of type 2 diabetes in adults, adolescents and children: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter-2 inhibitors, glucagon-like peptide-1 agonists, basal insulins, bolus insulins, and biphasic insulins, including analogues.

Scientific evidence of benefits

The application summarized results that answer two specific research questions:

1. For adults with type 2 diabetes on metformin monotherapy with inadequate glycaemic control, what is the comparative efficacy and safety of using a drug from one of the following classes as second-line agent:

   - sulfonylurea
   - insulin
   - DPP-4 inhibitor
   - GLP-1 agonist
   - SGLT-2 inhibitor?

2. For adults with type 2 diabetes, what are the comparative cardiovascular effects of drugs belonging to one of the following classes:

   - insulin
   - DPP-4 inhibitor
   - GLP-1 agonist
   - SGLT-2 inhibitor?

Question 1: Patients inadequately controlled on metformin

For the first research question, 175 unique RCTs and 78 companion publications were included in the systematic review. A total of 166 RCTs reported study outcomes of interest. References are reported in the original application.

Risk of bias was assessed for all studies using the Cochrane Collaboration's Risk of Bias tool. Included RCTs generally had a moderate risk of bias. RCTs commonly failed to adequately report their methods for random sequence generation and allocation concealment. At least 20% of the studies were assessed to be at high risk of bias due to incomplete reporting of efficacy or safety outcomes.

Overall assessment of the internal and external validity of the included RCTs noted limitations in several areas that have been highlighted in previous CADTH therapeutic reviews. This included the use of surrogate end-points (e.g. HbA1c) rather than more clinically meaningful end-points, limited sample sizes, and duration of follow-up. Many RCTs failed to register in a trial registry (such as Clinicaltrials.gov) or to publish a study protocol.

Poor reporting was a common issue across trials. Failure to report protocol definitions for study outcomes (e.g. hypoglycaemia), true intention-to-treat analyses (i.e. an analysis including all randomized patients), and dose and/or duration of stable metformin therapy before randomization. Many studies failed to adequately report details about the dosage of metformin background therapy during treatment.

Network meta-analyses (NMAs) were conducted for 18 outcomes for the reference case of class comparisons. The full results for all class comparisons, as well as model diagnostics for the fixed and random effects models, are presented in the appendices to the application.

For each outcome, the mean differences or odds ratios from the NMA of the reference case are provided, comparing each drug class added on to metformin background therapy with metformin monotherapy. Results for select head-to-head comparisons of interest (sulfonylurea, SGLT-2 and DPP-4 inhibitors, GLP-1 agonists, and insulins) are presented for each outcome where data were available.

Glycated haemoglobin (HbA1c)

Eighty-four RCTs reported mean change from baseline in HbA1c and were included in the reference case NMA.

Relative to metformin monotherapy, all of the selected classes significantly reduced mean difference in the change from baseline in HbA1c. When the classes were compared with each other, DPP-4 inhibitors did not reduce HbA1c as much as sulfonylureas, TZD or GLP-1 agonists (random effects model, **see Table A, page 386 of TRS**).

Body weight

Seventy RCTs reported changes from baseline body weight and were included in the reference case NMA.

Relative to metformin monotherapy, sulfonylurea, TZD and basal insulin combinations with metformin significantly increased mean body weight (range 2.1–2.8 kg) with no significant differences between these classes. SGLT-2 inhibitors and GLP-1 agonists added on to metformin were associated with significant reductions in mean body weight relative to metformin monotherapy (range –1.4 kg to –2.2 kg).

When the classes were compared, all non-insulin treatments added to metformin, except TZD, resulted in significant reductions in mean body weight relative to sulfonylurea (range –1. 9 kg to –4.3 kg). SGLT-2 inhibitors and GLP-1 agonists also resulted in significant reductions in mean body weight relative to DPP-4 inhibitors, while TZD and basal insulin resulted in significant increases in mean body weight from baseline. TZD, basal and biphasic insulin added to metformin significantly increased mean body weight from baseline relative to SGLT-2 inhibitors and GLP-1 agonists (**see Table B, page 387 of TRS**).

All-cause mortality, cardiovascular mortality and heart failure

Because of the low event rate and the large number of zero events in the data set, the NMA models for all-cause mortality, cardiovascular mortality and heart failure were not robust. Pairwise meta-analyses found no difference in the relative risks. The estimated confidence intervals were wide, again because of the paucity of events. No other direct estimates could be made.

Question 2: Patients at high risk for cardiovascular events

For question 2, 66 papers representing 17 unique RCTs were included in the systematic review. References are reported in the original application.

All but one of the studies were double-blind and all were funded by a pharmaceutical company. The sample size ranged from 304 to 16 492. The threshold baseline HbA1c level for inclusion in the trials was typically 6.5%, although some used a threshold as low as 6.0%. The mean baseline duration of diabetes ranged from 5.6 years to 13.4 years.

The included RCTs enrolled patients on various background therapies, and pragmatically allowed for continuation of whatever the existing background therapy was at baseline. In general, therefore, participants added the study intervention to their existing therapy. Background therapies were: no treatment (i.e. participants were drug-naïve when they started the study intervention); monotherapy (participants were taking a single antidiabetic medication or insulin and added the study intervention to that therapy); dual therapy; and combinations of more than two therapies. Monotherapy was predominantly metformin or insulin and dual therapy predominantly metformin plus a sulfonylurea or insulin.

Most studies enrolled participants at high risk of cardiovascular events or with cardiovascular disease. Mean body mass index (BMI) was between 25.2 (SD 3.0) and 32.5 (SD 6.3).

Most of the included RCTs were at overall low risk of bias. A total of 72% of RCTs were judged to be at low risk of bias for random sequence generation and allocation concealment. Since all the outcomes of interest were considered to be objective, all RCTs were judged to be at low risk of bias for outcome assessment. Most trials were judged to be at low risk of bias (67%) for incomplete outcome data.

While carrying out the risk of bias assessments, reviewers noted that there were some limitations that should be noted in the cardiovascular RCTS, including the use of outcome definitions that may deviate from what would be considered standard (EMPA-REG OUTCOME), and lack of control for type 1 error (LEADER and EMPA-REG OUTCOME, exploratory analyses were not adjusted for). Other concerns included protocol amendments made after an interim analysis (EMPA-REG OUTCOME) and a number of participants in the LEADER study who completed or discontinued the study before having an outcome after their last visit.

All-cause mortality

A total of 8 RCTs (*n* = 66 311) reported all-cause mortality and were included in the reference case analysis. Compared with placebo and DPP-4 inhibitors, SGLT-2 inhibitors – but none of the other treatments – reduced the risk of all-cause mortality (**see Table C, page 389 of TRS**).

Cardiovascular mortality

Six RCTs (*n* = 30 439) reported cardiovascular mortality and were included in the reference case analysis. Compared with placebo and with each other, none of the selected classes significantly lowered the risk of cardiovascular mortality (**see Table D, page 390 of TRS**).

Scientific evidence of harms

Question 1: Patients inadequately controlled on metformin

Severe hypoglycaemia

Severe hypoglycaemia was typically defined as an event requiring third-party assistance. Forty-eight RCTs reported severe hypoglycaemia and were included in the reference case NMA.

None of the classes significantly increased severe hypoglycaemia when compared with metformin monotherapy. When compared with each other, the GLP-1 agonists, SGLT-2 inhibitors and DPP-4 inhibitors significantly reduced the risk of severe hypoglycaemia relative to sulfonylureas (**see Table E, page 391 of TRS**).

Non-severe hypoglycaemia

The clinical definition of non-severe hypoglycaemia varied across the included RCTs. As in previous reviews, the most common differences were the specific blood glucose threshold for hypoglycaemia and whether patients were required to validate symptoms of hypoglycaemia with self-monitoring of blood glucose.

Sixty-seven RCTs reported at least one episode of non-severe hypoglycaemia and were included in the reference case NMA.

Compared with metformin monotherapy, the odds of non-severe hypoglycaemia were higher with sulfonylurea, basal and biphasic insulin. When the classes were compared, all except biphasic insulin significantly reduced odds of non-severe hypoglycaemia relative to sulfonylurea (**see Table F, page 393 of TRS**). Relative to DPP-4 and SGLT-2 inhibitors and GLP-1 agonists, basal and biphasic insulin significantly increased the odds of non-severe hypoglycaemia; moreover, biphasic insulin significantly increased the odds relative to basal insulin.

Severe adverse events

Sixty-six RCTs reported serious adverse events and were included in the reference case NMA. Data were available for all drug classes. Compared with metformin monotherapy and with each other, none of the classes significantly increased or decreased the odds of serious adverse events (**see Table G, page 394 of TRS**).

Question 2: Patients at high risk for cardiovascular events

Severe hypoglycaemia

Eight RCTs reported severe hypoglycaemia (*n* = 66 133) and were included in the reference case NMA. The percentage of participants with a severe hypoglycaemic event ranged from 0.3% to 3.3%. Compared with placebo, there was a significantly lower risk of severe hypoglycaemia with GLP-1 agonists but a significantly increased risk with TZD. There was a significantly lower risk of severe hypoglycaemia with

GLP-1 agonists relative to DPP-4 inhibitors. TZD significantly increased the risk of severe hypoglycaemic events relative to both DPP-4 inhibitors and GLP-1 agonists, but the risk was not significantly different from that with SGLT-2 inhibitors (**see Table H, page 395 of TRS**).

Severe adverse events

Six RCTs reported severe adverse events (*n* = 31 219) and were included in the reference case NMA. The percentage of people with serious adverse events ranged between 18% and 50%. Compared with placebo and with each other, none of the selected classes significantly differed in the risk of severe adverse events (**see Table I page 396 of TRS**).

Summary of evidence on benefits and harms

In synthesis, based on network meta-analyses, adjunctive second-line therapies were associated with possible reductions in glycaemic control when compared with metformin monotherapy, with few differences between any of the active treatments. Sulfonylurea and GLP-1 agonists reduced glycated haemoglobin when compared with DPP-4 inhibitors; GLP-1 agonists and sulfonylurea reduced weight when compared with metformin monotherapy, while insulin and sulfonylurea increased weight when compared with the other classes. GLP-1 agonists and insulins increased the number of adverse events and withdrawals. In high-risk patients, SGLT-2 inhibitors were possibly associated with a reduction in all-cause mortality when compared with placebo and with DPP-4 agonists and SGLT-2 inhibitors were not associated with severe hypoglycaemia events.

Sulfonylurea and insulins increased non-severe hypoglycaemia when compared with metformin monotherapy and other classes. However, basal insulin was associated with fewer non-severe hypoglycaemia events when compared with sulfonylurea.

WHO Guidelines

WHO guidelines on type 2 diabetes are being developed but had not been finalized at the time of the Expert Committee meeting.

Expert Committee recommendations

The Expert Committee acknowledged the wide coverage of the application, which compared all second-line therapies used in the intensification phase of therapy (i.e. between the initial therapy with metformin and any treatment combination containing insulin) in patients with type 2 diabetes.

The Committee noted that the application represents an advanced version of a report commissioned by the Canadian Agency for Drugs and Technologies in Health (CADTH). The Committee considered that data on the effectiveness of and harms caused by some of the medicines covered in the application will be supplemented in the coming years as new trials and longer follow-up are completed. **The Committee considered the evidence provided was insufficient to propose changes to the EML, which thus far includes only sulfonylurea as intensification therapy.**

The Committee confirmed the role of sulfonylureas as (one of) the most cost-effective treatment options for intensification therapy of type 2 diabetes.

The Committee noted that SGLT-2 inhibitors have been reported to be associated with a relevant clinical benefit as intensification therapy in patients at high risk of cardiovascular events, leading to a relevant reduction in overall mortality. This finding needs to be confirmed in other trials, before this class of medicines can be selectively supported for patients with type 2 diabetes.

On the basis of the evaluation, the Expert Committee did not recommend the inclusion of any additional medicines for second-line therapy of type 2 diabetes.

References

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2013 (including the 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2014 (WHO Technical Report Series, No. 985).
2. Second and third-line therapy for patients with diabetes (Optimal Use Project). Ottawa: Canadian Agency for Drugs and Technologies in Health; 2013 (https://www.cadth.ca/second-third-line-therapies-type-2-diabetes, accessed 28 March 2017).