Record of the Diabetes Advisory Committee Meeting held on 20 April 2023

Diabetes Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Diabetes Advisory Committee meeting; only the relevant portions of the meeting record relating to Diabetes Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Diabetes Advisory Committee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present
Elizabeth Dennett - Chair
Angela Renall (Zoom)
Bruce King
Diana McNeill (Zoom)
Elizabeth Dennett
Esko Wiltshire
Helen Lunt
Karen Mackenzie
Kate Smallman
Rinki Murphy
Christine Pihema

Apologies
Nic Crook
Sean Hanna

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Glucose solution with a biscuit	Cost neutral
• liraglutide in the treatment of obesity	Deferred
• Insulin degludec/insulin aspart (Ryzodeg) for diabetes mellitus (Type 1 or Type 2)	High

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Diabetes Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) 2021 and Specialist Advisory Committees 2021 .Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

3.3. The Diabetes Advisory Committee is a Specialist Advisory Committee of Pharmac. The Diabetes Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Diabetes Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for diabetes that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for diabetes that differ from the Diabetes Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Diabetes Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for diabetes.

4. Record of PTAC meeting held Monday, October 17, 2022

4.1. The Advisory Committee reviewed the records of the PTAC meeting held on 17 October 2022 and agreed that the minutes be accepted.

5. Previous action points/recommendations made

5.1. The Committee noted paragraph 4.7 in the 2021 Diabetes Advisory Committee records relating to SGLT-2 inhibitors and the risk of diabetic ketoacidosis (DKA) in the surgical setting. The Committee considered that while the anaesthetic and surgical communities had been engaged in the production of type II diabetes management guidelines, there was still a need to develop guidance for the surgical setting in New Zealand and that this should be done in partnership with these specialist groups.

6. Matters arising - Glucose solution with a biscuit (HypoPak) Kit including a biscuit

Application

6.1. The Advisory Committee reviewed the correspondence relating to an application for glucose solution with a biscuit (HypoPak) in the treatment of inpatient hypoglycaemic events.

6.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item

Recommendation

6.3. The Advisory Committee agreed with its previous **recommendation** that the glucose solution with a biscuit (HypoPak) be listed only if cost-neutral to the glucose gels listed on the Hospital Medicines List (HML) and considered that the addition of a biscuit did not justify additional expenditure from the Combined Pharmaceutical Budget.

6.4. The Advisory Committee considered that the addition of a biscuit to the already available sachets would not meaningfully improve the hospital management of hypoglycaemic events or prevent hypoglycaemic events from occurring.

Background

6.5. The (then) Subcommittee discussed the impact of funding glucose solution with a biscuit (HypoPak) for the inpatient treatment of hypoglycaemia at the Diabetes Subcommittee meeting in 2019

6.6. At that meeting, the Subcommittee recommended that "glucose solution plus complex carbohydrate, brand name HypoPak (15 g glucose sachet and a 20 g vanilla gluten, dairy, and egg free biscuit) be funded only if cost-neutral to the glucose with sucrose and fructose gel, 18 g sachet currently listed on the Hospital Medicines List (HML)."

6.7. In making this recommendation, the Subcommittee considered the following The Advisory Committee considered that the addition of a biscuit to the already available sachets would not meaningfully improve the hospital management of hypoglycaemic events or prevent hypoglycaemic events from occurring.

6.7.1. Where improvements were required for in hospital hypoglycaemic episode management, this could be addressed by changes in hospital systems and protocols while utilising the products currently listed on the HML.

6.7.2. That there is a lack of evidence demonstrating that access to HypoPak would improve the management and health outcomes of patients experiencing hypoglycaemia compared with currently listed options.

6.8. The Committee noted that as a result of the 2020/2021 annual invitation to tender, Pharmac decided to fund HypoPak's brand of 15g glucose (dextrose) sachets without the biscuits on the basis that these were cost-neutral to the other funded glucose sachets.

Discussion

6.9. The Committee noted a correspondence item that Pharmac has received from the supplier of the HypoPak brand of glucose sachets, which included additional evidence to support the ongoing health need for funding of HypoPak kits (the sachets accompanied by a pre-packaged biscuit) in Te Whatu Ora Hospitals.

6.10. The Committee noted that this additional evidence included clinical support letters, treatment guidelines for hypoglycaemia, and a clinician survey from Te Whatu Ora Hospitals.

6.11. The Committee noted treatment guidance issued relating to the management of hypoglycaemia (Lowe RN, Williams B, Claus LW. Diabetes: how to manage patients experiencing hypoglycaemia. Drugs Context. 2022;11:2021-9-11 https://doi.org/10.7573/dic.2021-9-11). The Committee noted that current best practice is to deliver a 15g dose of fast-acting glucose to treat a hypoglycaemic episode in a conscious adult, before waiting 15 minutes to re-test their blood glucose concentration. The Committee noted that a weight-based dose of 0.3g/kg of fast-acting glucose is recommended for children.

6.12. The Committee noted that the supplier had conducted a survey across Te Whatu Ora Hospitals to establish current management protocols for treating hypoglycaemic episodes. The Committee noted that the survey asked hospitals about the type of glucose preparation they used, the amount used, the time to their next test and any policy on whether a complex carbohydrate is used following fast-acting glucose.

6.13. The Committee noted that current management protocols for treating hypoglycaemic episodes did vary between Te Whatu Ora Hospitals but that they all have a protocol that was focussed on the initial deliver of fast-acting glucose. The Committee noted that many Te Whatu Ora Hospitals do not have policies around the time to next test, but that most were following-up the delivery of fast-acting glucose with a complex carbohydrate.

6.14. The Committee considered that a majority of hypoglycaemic episodes in the hospital occur due to delayed mealtimes. The Committee considered that the currently available glucose gels are appropriate for the acute correction of hypoglycaemia until the patient is able to receive a meal. The Committee considered that it would be common for complex carbohydrates to be available on the ward outside of mealtimes.

6.15. The Committee considered that the inclusion of the biscuit would not necessarily prevent the need for two 15g sachets of fast-acting glucose to be delivered, particularly where rapid correction of severe hypoglycaemia is required. Members considered there was a risk that the biscuit could impair the absorption of fast-acting glucose if used incorrectly.

6.16. The Committee noted that the biscuit is free of lactose and other common allergens and that this may provide a suitability advantage for those patients with food allergies or intolerances.

6.17. While the Committee considered there may be suitability benefits to combining the gel and biscuit within the same pack with clear instructions on how to use them, the Committee considered that these did not justify additional expenditure from the Community Pharmaceutical Budget.

7. Liraglutide for obesity (for patients with BMI 55kg per m^2 and over, with high cardiovascular risk, unable to access bariatric surgery or Māori or Pacific people with BMI 50kg per m^2 and over)

Application

7.1. The Advisory Committee reviewed the application for liraglutide in the treatment of obesity.

7.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

7.3. The Advisory Committee deferred its recommendation for liraglutide for the treatment of obesity (individuals with BMI 55 kg/m2 and over, with high cardiovascular risk, unable to access bariatric surgery; or Māori or Pacific people with BMI 50 kg/m2 and over, with high cardiovascular risk) pending consideration of the most appropriate target population for liraglutide.

7.4. The Advisory Committee considered the following in making this recommendation:

- The proposed group for funding was likely not the only group of people who would benefit from this treatment
- Evidence is not available to support the use of liraglutide in those with a BMI ≥55 kg/m2 or a BMI ≥50 kg/m2 for Māori or Pacific peoples or to support the restriction to people 35 to 44 years of age.
- A thorough review of the GLP-1 agonist class of medicines and their use across metabolic conditions was recommended.

Discussion

Māori impact statement

7.5. The Committee discussed the impact of funding liraglutide for the treatment of obesity on Māori health areas of focus and Māori health outcomes. The Committee considered that Māori were disproportionately affected by obesity. The Committee considered that currently funded, effective treatments for weight loss were limited to bariatric surgery and green prescription. The Committee considered that Māori are less likely to receive funded bariatric surgery than non-Māori and that there were geographic inequities in access to green prescription.

7.6. The Committee considered that there was a higher health need associated with obesity among Māori compared with non-Māori. The Committee noted that the risk of related complications differs between ethnic groups. The Committee considered that access to this treatment was likely inequitable due to systemic barriers that are faced by Māori. The Committee considered that appropriate access to funded effective weight loss treatments was important in not further

increasing inequities.

Background

7.7. The Committee noted that this application had been previously reviewed by PTAC at its November 2022 meeting where PTAC deferred making a recommendation pending: Te Whatu Ora engagement for policy and system change; development of Special Authority criteria that better reflect the unmet health need; and real world evidence of use in New Zealand for weight loss without significant concurrent lifestyle intervention.

7.8. The Committee noted that there were also global supply issues affecting GLP-1 agonists as a class of medicines, driven by increasing demand across a range of indications and limited manufacturing capacity. The Committee noted that these supply issues had impacted New Zealand. The Committee noted that due to a global shortage of dulaglutide, liraglutide (brand name Victoza) was funded from 1 March 2023 for people with diabetes that meet particular Special Authority criteria.

7.9. The Committee noted that although this liraglutide (brand name Saxenda) application was for the same drug as is currently funded for people with diabetes, the two brands and their Medsafe approvals differed by indication and dose.

Health need

7.10. The Committee considered that there was an unmet health need for those with a BMI ≥30kg/m^2, a group which would be classified as obese. The Committee noted that in 2020, 34.3% of New Zealand adults were considered obese (New Zealand Health Survey 2020/21). The Committee considered that the health need of those with extreme obesity, defined as having a BMI ≥50 kg/m^2, is very high and that people in this group were likely to have already developed cardiovascular or metabolic complications.

7.11. The Committee considered that the prevalence of obesity was higher among certain groups including people living in lower socioeconomic areas, Pacific peoples, Māori, people of South Asian ethnicity, and women particularly in rural areas. The Committee noted that among Māori and Pacific peoples, the mean age of onset of obesity-related complications such as cardiovascular disease was lower compared with non-Māori, non-Pacific people.

7.12. The Committee noted that obesity is associated with a wide range of health complications including cardiovascular disease, type 2 diabetes, osteoarthritis, cancer, respiratory disorders including sleep apnoea, and reproductive disorders. The Committee considered that a 5-10% weight loss improves cardiovascular outcomes. The Committee considered the stigma attached to obesity and noted that people living with obesity may experience social isolation and discrimination in a range of educational, workplace and social settings.

7.13. The Committee considered intergenerational impacts of obesity and noted the health need associated with obesity affected not just the individual but also family and whānau. The Committee noted that the food environment in early life has an impact on an individual's health across their life course. The Committee was aware anecdotally of young people caring for older family members living with complications related to severe obesity, additional to exposure to common food availability etc. within their households.

7.14. The Committee considered that conceptualisations of obesity as a health issue may differ across cultural communities within New Zealand. The Committee considered that culturally safe health services, and interventions tailored around whānau, were important to ensure that people living with obesity had the necessary support to reduce weight and minimise the risk of potential health

complications.

7.15. The Committee discussed the limited range of effective and currently funded weight loss interventions available in New Zealand. The Committee considered that bariatric surgery was one such intervention, and that demand for bariatric surgery was far greater than the available health system capacity to provide it. The Committee noted that the criteria for accessing publicly bariatric surgery vary across the country, and that wrap-around care is required before and after bariatric surgery. The Committee considered that Māori were less likely to receive funded bariatric surgery than non-Māori due to a range of access barriers. The Committee noted that people with a body mass of >300 kg were unable to access MRI/CT scanning, and this would affect their access to diagnostics, treatments and surgery they may require for other conditions.

7.16. The Committee also noted that there are no funded pharmaceutical weight loss treatments in New Zealand. The Committee considered the access unfunded weight loss pharmaceuticals is cost prohibitive and further increases health inequities between those able to afford treatment and those not. The Committee considered the alternative pharmaceutical options have worse adverse effect profiles than GLP-1 agonists.

7.17. The Committee considered that the effectiveness of weight loss interventions delivered in primary care was limited by the availability of trained practitioners and the significant individual input required to make meaningful change in the context of obesogenic food and exercise environments. The Committee considered that the current pressures experienced by primary care providers were not conducive to facilitating weight loss interventions. The Committee noted that there were geographic inequities in access to green prescription in New Zealand.

7.18. The Committee discussed the impact of the rising cost of living and the obesogenic food environment in New Zealand and noted that high food prices disproportionately affected those of lower socioeconomic status. The Committee noted that when healthier foods are expensive and less accessible, this affects peoples' ability to manage their weight through food intake.

7.19. The Committee considered that, in addition to medicines, a range of health system and public policy changes were needed to address the high prevalence of obesity and obesity-related complications in New Zealand. The Committee considered that it was important to ensure that funding new weight loss treatments did not widen current inequities in the burden of obesity.

Health benefit

7.20. The Committee that its previous consideration of the health benefits of GLP-1 agonists was extensive in terms of the cardiovascular, renal and glycaemic effects, but the Committee had not considered GLP-1 agonists for weight loss specifically.

7.21. The Committee noted PTAC's consideration of the evidence for weight loss benefit supplied by the applicant in the initial application for funding, and noted the following clinical trials:

- Pi-Sunyer et al. N Engl J Med. 2015;373:11-22
- le Roux et al. Lancet. 2017;389:1399-409
- Fujioka et al. Obesity (Silver Spring). 2016;24:2278-88
- Le Croix et al. Obes Facts. 2017;10:531-44

7.22. The Committee noted PTAC's consideration of the evidence regarding adverse events supplied by the applicant in the initial application for funding, and noted the following trials:

- Steinberg et al. Diabetes Care. 2017;40:839-48
- Wilding et al. Diabetes Obes Metab. 2016;18:491-9
- von Scholten et al. J Diabetes Complications. 2017;31:1164-8

7.23. The Committee noted that there were no New Zealand participants in the pivotal trials, but considered this was similar to other therapeutic settings, where extrapolation of the clinical trial data to the New Zealand context was required.

7.24. The Committee noted the supplier-proposed target population for liraglutide of 'individuals with BMI 55 kg/m2 and over, with high cardiovascular risk, unable to access bariatric surgery: or Māori or Pacific people with BMI 50 kg/m2 and over'. The Committee noted that there was a lack of evidence to inform the magnitude of treatment benefit that liraglutide offered for this group and considered that the available trial evidence noted could not be reliably extrapolated to this group.

7.25. The Committee was made aware of cases reporting efficacy in those with a BMI ≥50kg/m2. The Committee considered that systematic evidence of efficacy in people with a BMI ≥50kg/m2 was lacking.

7.26. The Committee considered that treatment of obesity using liraglutide would be long-term given that obesity is a chronic condition requiring ongoing management. The Committee noted evidence that cessation of liraglutide treatment after two years was associated with weight re-gain.

7.27. The Committee considered that there were likely to be differences in efficacy between different GLP-1 agonists, with regard to weight loss, but noted that trials of GLP-1 agonists in the setting of weight loss generally reported this class of medicines to be efficacious with a well-document side effect profile (Trujillo et al. Ther Adv Endocrinol Metab. 2015;6:19-28).

Suitability

7.28. The Committee noted that within the class of GLP-1 agonists, there were differences in frequency of injections between agents. The Committee noted that liraglutide is administered daily through a prefilled disposable pen, compared with weekly with some other GLP-1 agonist agents. The Committee considered this to be an important suitability consideration as more frequent injections may affect adherence to therapy.

7.29. The Committee considered the environmental impact of prefilled disposable pens to be more than other treatments such as tablets or capsules.

Cost and savings

7.30. The Committee noted that setting a lower BMI eligibility threshold for liraglutide than the supplier has proposed would enable a greater number of individuals to be eligible for this treatment. The Committee considered that some individuals living with obesity were already eligible for treatment with liraglutide as they had diabetes and met current Special Authority criteria, but that the funded liraglutide formulation (brand name Victoza) had a lower daily dose than the liraglutide (brand name Saxenda) formulation for weight loss considered in this proposal. The Committee noted the current funding restrictions for diabetes limited the dose of liraglutide to 1.8 mg daily compared to the 3 mg daily dose indicated for weight loss. The Committee considered that there would likely be patients with type 2 diabetes that would also benefit from treatment at a higher dose.

7.31. The Committee considered that if liraglutide was funded there would be minimal impact on the number of bariatric surgery procedures delivered, as these services were already at capacity.

7.32. The Committee considered that weight loss may enable people to become eligible for other surgery such as hip replacements and knee replacements and that by maintaining an individual's mobility these surgeries could support future stabilisation of weight or weight loss, but that the magnitude and materiality of these impacts was hard to quantify.

7.33. The Committee noted that, in addition to cardiovascular and diabetes complications, people with obesity were also at risk of complications related to cellulitis. The Committee considered that some individuals may require less frequent hospitalisation for cellulitis if they experienced significant weight loss.

Funding criteria

7.34. The Committee noted the National Institute of Clinical Excellence (NICE) guidance 2020 recommended for England/Wales funded liraglutide use in adults combining all of BMIs either at least 35kg/m2 or at least 32.5kg/m2 for ethnic groups at higher risk of complications plus non-diabetic hyperglycaemia and cardiovascular disease based on risk factors such as hypertension and dyslipidaemia plus prescribed by a secondary care specialist in a tier 3 weight management service and used alongside a reduced-calorie diet and increased physical activity.

7.35. The Committee noted the Canadian Agency Drug and Technologies in Health (CADTH) was not able to conclude that the use of liraglutide reduced comorbidities caused by obesity and had recommended it not be funded for chronic weight management in adults.

7.36. The Committee noted the Scottish Medicines Consortium (SMC) approved use of liraglutide in those with a BMI ≥35kg/m^2 with pre-diabetes or high cardiovascular risk, and had commented on the reported waning effect of liraglutide on weight loss over time.

7.37. The Committee discussed the supplier's proposed target patient population of "*individuals with BMI 55kg/m^2 and over, with high cardiovascular risk, unable to access bariatric surgery; or Māori or Pacific people with BMI 50kg/m^2 and over*". The Committee considered that the appropriate target population for liraglutide should be wider than proposed by the supplier, because of the high health need associated with obesity in New Zealand and the potential for greater individual health benefit if liraglutide was funded for a wider range of groups.

7.38. The Committee noted the current funding of liraglutide was confined to people with diabetes (with hypoglycaemic and cardiovascular therapeutic intent, not necessarily weight loss) but was provided as a lower daily-dose formulation, and was unable to identify evidence that the lower daily dose formulation provided at least the same weight loss as the higher dose liraglutide (Saxenda) formulation applied for. The Committee therefore agreed it appropriate the eligibility criteria for weight loss in obesity include people with diabetes, not effectively exclude people experiencing obesity who have diabetes.

7.39. The Committee considered that groups with the greatest potential to experience a treatment benefit from liraglutide included:

- People with pre-diabetes
- People at high risk of cardiovascular disease, without pre-existing cardiovascular disease

- People at risk of other obesity-related complications.
- People who, due to their obesity, are unable to access surgical intervention and/or imaging.

7.40. The Committee considered that there were some groups who may not necessarily be included in a Special Authority with simple BMI and age thresholds, and noted that the following target groups could be considered for eligibility:

- People with conditions that result in significant secondary weight gain e.g., hypothalamic obesity in children with brain tumours
- Young people with prediabetes who are at risk of developing type 2 diabetes and/or other complications from obesity
- People who could receive liraglutide as a bridge to bariatric surgery or joint replacement surgery, but whose BMIs extend beyond the safe upper limits for those procedures, making those procedures inaccessible to them.

7.41. The Committee considered that the age and BMI thresholds in the Special Authority criteria proposed by the supplier were not supported by current evidence. The Committee also considered that the ethnicity-specific age and BMI thresholds did not reflect the groups among Māori and Pacific communities with the highest health need. The Committee noted that decisions around the appropriate target population for liraglutide could include consideration of lower BMI thresholds for eligibility, focussing on individuals with risk factors for obesity-related complications, and the removal of age-based access criteria.

7.42. The Committee considered that if liraglutide were to be funded for weight loss in New Zealand, the access criteria should aim not to further widen ethnic inequities in access to funded weight loss treatments. The Committee considered that equitable uptake of liraglutide among Māori and Pacific peoples was important for addressing the disproportionate impact of obesity and obesity-related complications they experience. The Committee noted that ethnicity-based access criteria could be explored as an affirmative action to support equitable uptake.

7.43. The Committee considered that the use of BMI would be a practical measure to set a threshold to define the eligible group, acknowledging its limitations. The Committee considered that the use of other measurements such as waist circumference were less appropriate as they were difficult to obtain in clinical practice and there would be issues with setting an appropriate eligibility threshold.

7.44. The Committee discussed the appropriateness of restricting the use of liraglutide to those who were enrolled in a Tier 3 service, a wraparound metabolic service delivered by a multidisciplinary team of clinical practitioners. The Committee considered these types of services do not exist throughout New Zealand, with the first of these services being set up at Te Whatu Ora in Counties Manukau (where evaluation of this will inform any expansion to other public services). The Committee considered that restricting use of liraglutide to those who were enrolled in a Tier 3 service was inappropriate as it would further widen geographic inequities to weight loss interventions.

Summary for assessment

7.45. The Advisory Committee considered that elements of in the PICO (population, intervention, comparator, outcomes) for this application are unclear/uncertain at this time. The PICO will be developed based on additional clinical advice sought by Pharmac staff.

8. Insulin degludec/insulin aspart (Ryzodeg)in the treatment of diabetes mellitus (type 1 or type 2).

Application

8.1. The Advisory Committee reviewed the application for Insulin degludec/insulin aspart (Ryzodeg)in the treatment of diabetes mellitus (type 1 or type 2).

8.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

8.3. The Advisory Committee **recommended** that insulin degludec/insulin aspart be funded, without restriction, with a **high** priority within the context of treatment of diabetes.

8.4. The Advisory Committee recommended this due to suitability factors (no resuspension required, flexibility of dose timing) and likely reduction in the risk of hypoglycaemia compared to biphasic insulin aspart.

Discussion

Māori impact

8.5. The Committee discussed the impact of funding insulin degludec/insulin aspart (Ryzodeg) for the treatment of diabetes mellitus (type 1 or type 2) on Māori health areas of focus and Māori health outcomes. The Committee noted type 2 diabetes disproportionally affects Māori, with Māori 2.5 times more likely to have type 2 diabetes than their European ethnicity counterparts, with a prevalence of 7.5% compared to the national average of 4.7% (Holder-Pearson et al. Front Med, 2022;9;756223). In addition to increased prevalence, Māori have an earlier age of onset and a higher risk of diabetes related complications (Yu et al. Lancet Glob Health. 2021;9:e209-17). These complications can include that Māori are 2.8 times more likely than non-Māori to have renal failure, and 1.7 times more likely to have a lower limb amputation than non-Māori (Beaton et al. Int J Equity Health. 2019;18:3).

8.6. The Committee noted Māori experience a disproportionate burden of diabetes-related adverse outcomes compared to other ethnicities. Among people aged 16 and younger with type 1 diabetes, Māori had a greater mean glycated haemoglobin (HbA1c), compared to people of European ethnicity (9.1% versus 8.1%, $p<0.001$) (Carter et al. Diabetologica. 2008;51:1835-42). The Committee noted that higher HbA1c values are associated with a greater risk of microvascular and macrovascular complications (Diabetes Subcommittee, September 2021**)**.The Committee noted that Ministry of Health evidence reported that in the year 2018/9, Māori comprised 23.1% of publicly funded discharges for type 1 diabetes-related complications (Ministry of Health. National Minimum Dataset. 2021).

8.7. The Committee noted that overall there is a higher rate of death attributed to diabetes in New Zealand Māori compared to non-Māori populations (34.2 vs 8.1 per 100,000 respectively) (Manatū Hauora, Mortality web tool. 2018: New Zealand).

8.8. The Committee noted that additional benefits to Māori maybe hard to quantify but a reduction in the number of doses of insulin required, and the amount, may be beneficial. In addition, the insulin weight gain associated with insulin degludec and insulin aspart appeared to be neutral in comparison to insulin glargine.

Background

8.9. The Committee considered the use of insulin degludec and insulin aspart (Ryzodeg) for the treatment of type 1 and type 2 diabetes in the community.

Health need

8.10. The Committee noted that type 1 diabetes is a chronic disease resulting from the autoimmune destruction of pancreatic beta-cells in the islets of Langerhans, which results in insulin deficiency. This endogenous insulin deficiency leads to hyperglycaemia, and the potential to develop life-threatening ketoacidosis. Although the aetiology of type 1 diabetes is not fully delineated, the disease is believed to develop when environmental factors in genetically susceptible individuals trigger T-cell activity, resulting in the pancreatic beta cell destruction. Type 1 diabetes is a life-long disease.

8.11. The Committee noted that type 2 diabetes mellitus is a chronic disease categorised by hyperglycaemia, which occurs due to insufficient production of insulin, or an ineffective response to the insulin the body produces.

8.12. The Committee noted the incidence and prevalence of type 1 and type 2 diabetes is increasing internationally, which is also observed in New Zealand.

8.13. The Committee noted data from Ministry of Health which reported that approximately 264,000 people in New Zealand have been diagnosed with diabetes, of which type 1 diabetes accounts for 5-10% of all cases (Manatū Hauora 2022, Te Tāhū Hauora - Health Quality & Safety Commission New Zealand, 2020), with an estimated 228,000 in New Zealand diagnosed with type 2 diabetes.

8.14. The Committee noted the Pearson et al. Front Med (Lausanne), 2022;10:756223 study, which reported those with type 2 diabetes accounted for 4.7% of the New Zealand population, which is projected to increase to up to 7.4% of the population by 2040.

8.15. The Committee noted data supplied from the Virtual Diabetes Register (VDR) (Manatū Hauora, virtual diabetes register and web tool. 2021: New Zealand) which estimated that in 2021 there were 292,365 people with diabetes in New Zealand. Of these 48,611 (17%) were Māori, 40,672 (14%) were Pacific, 22,375 (8%) were Indian and 180,707 (62%) were European and other. The prevalence of diabetes in New Zealand has been increasing since 2011 across all ethnic groups (Ministry of Health. 2021).

8.16. The Committee noted that acute clinical manifestations of type 1 diabetes are those related to both treatment-related hypoglycaemia (low blood sugar) and hyperglycaemia. Severe hypoglycaemia is an acute event that can result in seizure and coma and is a medical emergency. Hyperglycaemia, which exceeds the renal threshold to result in polyuria, increased thirst, dehydration, electrolyte disturbances, weight loss, and metabolic decompensation. In extreme cases this can result in diabetic ketoacidosis and non-ketonic hyperosmolar coma.

8.17. The Committee noted that the majority of those with type 2 diabetes are asymptomatic, and hyperglycaemia is noted on routine laboratory evaluation, prompting further testing. Classic symptoms of hyperglycaemia include polyuria, polydipsia, nocturia, blurred vision, and weight loss (Inzucchi et al. 2023, UptoDate).

8.18. The Committee noted that chronic complications for both type 1 and type 2 diabetes are macrovascular (coronary artery disease, cardiovascular disease, amputations) and microvascular (retinopathy, nephropathy, neuropathy). The Committee noted the Yau et al. 2021, Etiology and Pathogenesis of Diabetes Mellitus in Children and Adolescents study suggesting both the acute and chronic complications are inversely correlated to the degree of metabolic control achieved.

8.19. In addition, the Committee noted that diabetes has also been found to be associated with depression, as the impact of dealing with a lifelong chronic condition can be overwhelming and negatively impact the individual's mental health. The Committee considered evidence from Diabetes Australia. Depression and mental health. 2022 that estimated that up to 50% of people with diabetes also have a mental illness such as depression or anxiety, and that having diabetes more than doubles the risk of developing depression. Consequently, people with depression and diabetes may have difficulties in managing and controlling their glycaemic levels.

8.20. The Committee noted the Shamshirgaran et al. BMC Endocr Disord. 2020;20:32 study of older people with diabetes in New Zealand, which reported that diabetes was associated with reduced quality of life.

8.21. The Committee noted that uncontrolled diabetes can have a significant impact on the individuals' mortality due to its effect on heart disease, stroke, kidney failure, blindness, and lower limb amputation. The World Health Organization (WHO) estimates that between 2000 and 2019 there was a 3% increase in age-standardised mortality rates from diabetes (World Health Organization. 2022).

8.22. The Committee noted that caring for an individual with type 1 diabetes places a substantial burden on family and whānau. Management requires daily responsibilities and coordination of care between specialists, primary care, and day-care/school. Families of children with type 1 diabetes report having to restrict work hours, spending significant time caring/coordinating care, and experience significant financial burden. Families and caregivers may also experience social impacts, significant disruption, and emotional distress.

8.23. The Committee noted the Diabetes New Zealand Stigma Survey that highlighted that one in three respondents under the age of 65 reporting that having type 2 diabetes made them feel 'ashamed' or 'a failure'. The Committee further noted that the physical and psychological impacts of type 2 diabetes can have a detrimental impact on a person's ability to fully participate in the workforce as it contributes to work loss through absenteeism and health-related work limitations in the workplace and can ultimately reduce employment, impacting the person and their whānau (World Health Organization. Diabetes Key Facts. 2022).

8.24. The Committee noted that type 1 diabetes is likely more prevalent in New Zealand European ethnicity than Māori, for example the crude period prevalence of type 1 diabetes in 2012-2016 in Māori being 10.1% of all (Wheeler et al. NZMJ. 2019;132:1491), and in children aged <15 years Māori comprising just 18% of all children with type 1 diabetes (Burnside et al. Lancet Reg Health West Pac. 2022;31:100644), contrasting with Māori comprising 27% of all children. However, of people with type 1 diabetes, Māori experience a disproportionate burden of diabetes-related adverse outcomes compared to other ethnicities.

8.25. The Committee noted diabetes is also known to disproportionally affect Pacific peoples and those of South Asian ethnicities, with the highest rate of diabetes

found in those of an Indian ethnicity (11%) followed by Pacific peoples (9.6%).

8.26. The Committee considered the Holder-Pearson et al. Front Med, 2022;9;756223 study, which reported that lower household income alone is correlated with double the risk of type 2 diabetes. This study reported that this could be attributed to the increased barriers to lifestyle modifications (such as weight loss, increased exercise and dietary changes), and access and affordability of health care, which are key in the management of diabetes.

Health benefit

8.27. The Committee noted that insulin degludec/insulin aspart is a co-formulation of rapid-acting insulin aspart and ultra-long-acting insulin degludec. Insulin degludec forms a depot which is continuously and slowly absorbed leading to stable blood glucose lowering. It does not interfere with the rapid-acting insulin aspart.

8.28. The Committee noted that there was no other ultralong-acting insulin available in New Zealand. The Committee noted that the duration of action of insulin degludec was >42 hours.

8.29. The Committee noted that regulatory approval from Medsafe is pending for the indication of diabetes mellitus.

8.30. The Committee noted that other formulations of long-acting insulin including glargine have a variation in their peak to trough action, whilst it is anticipated that daily dosing of a ultralong acting insulin would have a smoother pharmacodynamic profile. Infrequent dosing of insulin degludec twice a week would result in a variation in peak to trough action.

8.31. The Committee noted that this smoother profile could result in a reduction in hypoglycaemia, and in particular overnight hypoglycaemia, as well as a reduction in the frequency of dosing, and improved flexibility in administration timing.

8.32. The Committee noted that there were some important concepts to consider when interpreting treat-to-target insulin randomised control trials (Garber et al. Diabetes Obes Metab. 2014;16:193-205). The Committee noted treat-to-target trial designs compare a 'new' insulin with an approved or commonly used insulin. Treat-to-target trials force-titrate insulin dosages to achieve a prespecified treatment goal. With comparable glycaemic control (traditionally measured using HbA1c), comparisons between different insulins of non-glycaemic effects such as hypoglycaemia frequency and weight change can be made. This allows assessment of the risk-benefit profile of the new insulin. The Committee noted that as treat-to-target randomised control trial design provides limited information about glycaemic efficacy, information about both glycaemic efficacy and non-glycaemic effects is therefore best interpreted using both treat-to-target randomised control trials and real-world studies.

8.33. The Committee noted that forced insulin dose titration studies are highly informative, however within a diabetes context (where peoples experience and non-physiological factors can influence them administering insulin day-to-day and in turn influence clinical outcomes), they do not provide definitive results, and may not translate into the real-world setting. The studies provide insights into comparative physiological effects and adverse events of different insulins.

8.34. The Committee noted that many trials use hypoglycaemic events as an endpoint, however that definitions of hypoglycaemia and events vary.

8.35. The Committee considered the Fulcher.et al. Diabetologia 2013, 56: S419-S420 Conference poster and Fulcher et al. Diabetes Care, 2014;37:2084-90 studies that compared the administration of twice daily insulin degludec/insulin aspart

(IDegAsp) to biphasic insulin aspart 30 (BIAsp 30) in those with inadequately controlled type 2 diabetes.

8.35.1. At 26 weeks, mean HbA1c was 7.1% for both groups, within the prespecified non-inferiority margin for mean change in HbA1c from baseline (primary endpoint; estimated treatment difference -0.03%-points, 95% CI -0.18; 0.13).

8.35.2. IDegAsp was superior in lowering fasting plasma glucose compared with BIAsp 30 (estimated treatment difference -1.14 mmol/L, 95% CI -1.53; -0.76, p<0.001) by the end of the trial.

8.35.3. Final mean daily insulin dose was 1.08 U/kg for IDegAsp and 1.20 U/kg for BIAsp 30 (estimated rate ratio [RR] 0.89, 95% CI 0.83; 0.96, p=0.002).

8.35.4. The authors reported significantly less confirmed hypoglycaemia episodes (self-reported plasma glucose (PG) <3.1 mmol/L or severe episode requiring assistance) per year for IDegAsp compared with BIAsp 30: 9.7 vs 14.0 respectively (estimated RR: 0.68, 95% CI 0.52; 0.89, p=0.0049), as well as significantly lower rates of nocturnal confirmed hypoglycaemia episodes, including during the maintenance period (post 16 weeks of treatment).

8.36. The Committee noted that the study population excluded those that had experienced a history of recurrent severe hypoglycaemia (defined as more than one severe hypoglycaemic event in the past 12 months). The Committee also noted that the levels of 4-5mmol/L to be a relatively low target to achieve prior to meals.

8.37. The Committee noted that the reduction in hypoglycaemic events was clinically meaningful but that the atmosphere of the trial was artificial, and hard to compare directly to a real-world environment.

8.38. The Committee considered the Christiansen et al. Diabetologia, 2013,56:S420 and Kaneko et al. Diabetes Res Clin Pract. 2015,107:139-47 randomised, open-label, treat-to-target phase 3 trials that compared the administration of twice daily insulin degludec/insulin aspart (IDegAsp) to biphasic insulin aspart 30 (BIAsp 30) in Asian people with poorly controlled type 2 diabetes.

8.38.1. At 26 weeks mean HbA1c was 7.1% for IDegAsp and 7.0% for BIAsp 30 IDegAsp was noninferior (predefined margin 0.4%) to BIAsp 30 for mean change in HbA1c from baseline (primary endpoint) as expected in a treat-to-target trial (estimated treatment difference IDegAsp-BIAsp 30: 0.05%-points, 95% CI -0.10; 0.20).

8.38.2. IDegAsp superior to BIAsp 30 in lowering fasting plasma glucose (FPG) (estimated treatment difference -1.06 mmol/L, 95% CI -1.43; -0.70, p<0.001), levels reduced to 5.4 mmol/L and 6.5 mmol/L, respectively at 26 weeks Mean daily insulin dose after 26 weeks: 0.79 U/kg for IDegAsp and 0.99 U/kg for BIAsp 30 (estimated rate ratio [RR] 0.79, 95% CI 0.73; 0.85, p<0.0001).

8.38.3. The confirmed rate of hypoglycaemia (self-reported PG <3.1 mmol/L or severe episode requiring assistance) was similar for IDegAsp and BIAsp 30 (9.6 episodes/y vs 9.5 episodes/y, estimated RR 1.00, 95% CI0.76; 1.32, p=ns).

8.38.4. Rate of nocturnal confirmed hypoglycaemia (onset from 00.01 to 05.59) was numerically (33%) lower with IDegAsp (estimated RR 0.67, 95% CI 0.43; 1.06, p=ns).

8.38.5. The rate of severe hypoglycaemia was not significantly different for IDegAsp and BIAsp (0.05 and 0.03 episodes/y, estimated RR 1.3, 95% CI 0.24; 7.03, p=ns). Maintenance period (post-16 weeks treatment): trend towards lower overall confirmed (estimated RR 0.84, 95% CI 0.6; 1.19, p=ns). Nocturnal confirmed (estimated RR 0.70, 95% CI 0.39; 1.26, p=ns) and severe (estimated RR 0.69, 95% CI 0.05; 9.8 p=ns) hypoglycaemia rates were similar for IDegAsp vs BIAsp 30. There was no difference in observed adverse event (AE) rates between treatment groups.

8.39. The Committee considered the Kumar et al. Diabet Med. 2017;34:180-8 open-label randomised phase 3 study in those with type 2 diabetes where the condition is inadequately controlled. The study compared insulin degludec/insulin aspart (IDegAsp) lonce daily vs insulin glargine (IGlar). At 26 weeks IDegAsp once daily was non-inferior to IGlar once daily in reducing HbA1c [mean estimated treatment difference IDegAsp once daily − IGlar once daily: −0.03% (95% CI −0.20, 0.14)].The evening meal glucose increment was significantly lower with IDegAsp once daily vs IGlar once daily [estimated treatment difference IDegAsp once daily − IGlar once daily: −1.32 mmol/l (95% CI −1.93, −0.72); P < 0.05]. The overall confirmed hypoglycaemia rate was higher with IDegAsp once daily (estimated RR 1.43; 95% CI 1.07, 1.92; P < 0.05). The rate of nocturnal hypoglycaemia did not significantly differ between the IDegAsp and IGlar groups [estimated RR 0.80 (95% CI 0.49, 1.30); not significant].

8.40. The Committee considered the Yang et al. Diabetes Obes Metab. 2019;21:1652-60. open-label, treat-to-target, 2:1 randomised trial in Chinese people with type two diabetes, comparing insulin degludec/insulin aspart (IDegAsp) versus biphasic insulin aspart 30 (BIAsp 30).

8.40.1. At 26 weeks mean HbA1c were similar between IDegAsp: 52 mmol/mol [6.95%] compared to BIAsp 30: 53 mmol/mol [7.01%]. Non-inferiority for HbA1c was confirmed for IDegAsp twice daily versus BIAsp 30 twice daily with respect to change from baseline to week 26, with an estimated treatment difference of −0.08% (95% CI −0.20; 0.05; P < 0.0001).

8.40.2. Mean fasting plasma glucose levels at week 26 were lower in the IDegAsp group compared with the BIAsp 30 group (6.07 vs. 7.48 mmol/L; Superiority in fasting plasma glucose, with respect to change from baseline after 26 weeks of treatment, was confirmed for IDegAsp twice daily versus BIAsp 30 twice daily, with an estimated treatment difference of −1.42 mmol/L (95% CI −1.74; −1.10; P < 0.0001).

8.40.3. An increase in body weight in both treatment groups: least squares (LS) mean (SE) change from baseline to week 26 of 2.82 (0.14) kg for IDegAsp twice daily and 2.21 (0.19) kg for BIAsp 30 twice daily; superiority of IDegAsp twice daily over BIAsp 30 twice daily was not shown (estimated treatment difference 0.61 [95% CI 0.15; 1.08]; P = 0.9954).

8.40.4. At baseline groups received similar mean insulin doses. At week 26, daily insulin dose (U/kg, mean [SD]) was numerically lower by 20% in those who received IDegAsp twice daily versus BIAsp 30 twice daily (0.78 [0.35] vs. 0.95 [0.35] U/kg; dose ratio 0.80). Higher mean (U/kg, mean [SD]) insulin doses were used pre-breakfast compared with pre-main evening meal in both treatment groups, both at baseline (IDegAsp twice-daily: 0.28 [0.12] vs. 0.25 [0.10] U/kg; BIAsp 30 twice daily: 0.28 [0.11] vs. 0.25 [0.10] U/kg, respectively), and at week 26 (IDegAsp twice daily: 0.48 [0.22] vs. 0.30 [0.18]; BIAsp 30 twice daily: 0.53 [0.19] vs. 0.42 [0.18], respectively).

8.40.5. Rates of nocturnal confirmed hypoglycaemic episodes per 100 participant-years of exposure (PYE) 34.9 vs. 61.0 with IDegAsp twice daily and BIAsp 30 twice daily, respectively. Rates of total confirmed hypoglycaemic episodes were 237.2 vs. 412.2 per 100 PYE with IDegAsp twice daily and BIAsp 30 twice daily, respectively. Similar rates of nocturnal confirmed and total confirmed hypoglycaemic episodes were observed between treatment groups for the first 8 weeks of the study, after which the groups diverged, with a higher number of episodes reported in the BIAsp 30 group compared with the IDegAsp group, up to week 26. Rates of nocturnal confirmed and total confirmed hypoglycaemic episodes were 47% and 43% lower respectively with IDegAsp twice daily than with BIAsp 30 twice daily (nocturnal confirmed hypoglycaemia estimated treatment difference 0.53 [95% CI 0.33-0.87]; P = 0.0056, total confirmed hypoglycaemia estimated treatment difference 0.57 [95% CI 0.42-0.77]; P = 0.0001), indicating superiority of IDegAsp twice daily for these endpoints.

8.41. The Committee considered the Hirsch et al. Diabetologia, 2011;54:S427 randomised phase 3 study that compared insulin degludec/insulin aspart (IDegAsp) or insulin detemir in those with type 1 diabetes where the condition is not adequately controlled.

8.41.1. The Committee noted that at 26 weeks, IDegAsp and detemir treatment resulted in similar improvements in HbA1c (0.73 %-point reduction for IDegAsp vs. 0.68 %-point reduction for detemir, estimated treatment difference IDegAsp-detemir: -0.05 %-point [95% CI: -0.18; 0.08]). Fasting plasma glucose was reduced by 1.6 mmol/l with IDegAsp and by 2.4 mmol/l with detemir; estimated treatment difference IDegAsp-detemir: 0.23 mmol/l [-0.46; 0.91] p=0.52). At 26 weeks mean total daily insulin doses 0.86 U/kg vs. 1.00 U/kg, for IDegAsp and detemir groups, respectively.

8.41.2. Mean body weight had increased from 76.5 to 78.9 kg (IDegAsp) vs. 76.1 to 77.5 kg (detemir); less weight gain in the detemir group compared with the IDegAsp group (estimated treatment difference: IDegAsp-detemir: 1.0 kg [0.38; 1.69] p=0.0021).

8.41.3. Confirmed hypoglycaemia (PG <3.1 mmol/l or severe) was reported for 94% of subjects in both groups; rates were similar (39 vs. 44 episodes/patient-year; estimated RR IDegAsp/IDet: 0.91 [95% CI: 0.76; 1.09] p=0.27). The rate of nocturnal confirmed hypoglycaemia (confirmed hypoglycaemia occurring between 00:01-05:59 h) was 37% lower with IDegAsp (3.7 vs. 5.7 episodes/patient-year; ERR: 0.63 [95% CI: 0.49; 0.81] p=0.0003).

8.41.4. The Committee noted that the study was designed to be similar to a multiple daily injection setting, where the combination insulin degludec/insulin aspart (IDegAsp) or insulin detemir were administered to regulate levels in relation to

the main meal, typically dinner, with additional insulin aspart with other meals as necessary. The Committee noted that those who had undergone severe hypoglycaemic events, or hypoglycaemic unawareness, were excluded from the trial. The Committee considered that this is not representative of the wider population indicated.

8.41.5. The Committee also noted that there were differences of appearance in the two insulins which makes blinding of the study difficult.

8.41.6. The Committee noted that the target glucose levels of 4-5mmol/L before meals to be not representative of the real-world target levels with regards to the administration of insulin.

8.42. The committee noted that random controlled trials using insulin detemir in one arm of the study commonly show weight loss for the detemir arm. The committee also noted that detemir was not funded in New Zealand. The Committee considered that it would be anticipated that forced dose titration studies using detemir in one arm and a long-acting insulin such as degludec in the other arm, would favour weight loss in the detemir arm.

8.43. The Committee considered the Hirsch et al. Diabetes Care. 2012;35:2174-81 randomised phase 3 study that compared insulin degludec/insulin aspart (IDegAsp) or insulin detemir and insulin aspart (IDet IAsp).

8.43.1. At 26 weeks, non-inferiority for IDegAsp versus IDet IAsp I was confirmed; HbA1C improved by 0.75% with IDegAsp and 0.70% with IDet IAsp to 7.6% in both groups (estimated treatment difference IDegAsp –determir: -0.05% [95% CI -0.18 to 0.08]).

8.43.2. Weight gain was 2.3 and 1.3 kg with IDegAsp and IDet IAsp, respectively ($P < 0.05$).

8.43.3. Total insulin dose was 13% lower in the IDegAsp group ($P < 0.0001$). No statistically significant difference between IDegAsp and IDet IAsp in the rates of severe hypoglycaemia (0.33 and 0.42 episodes/patient-year, respectively) or overall confirmed (plasma glucose <3.1 mmol/L) hypoglycaemia (39.17 and 44.34 episodes/patient-year, respectively).

8.43.4. Nocturnal confirmed hypoglycaemia rate was 37% lower with IDegAsp than IDet IAsp (3.71 vs. 5.72 episodes/patient-year, $P < 0.05$.

8.44. The Committee considered the Hirsch et al. Diabet Med. 2017;34:167-73 study in people with type 1 diabetes, that compared insulin degludec/insulin aspart (IDegAsp) + insulin aspart (IAsp) vs insulin detemir and insulin aspart (IDet+IAsp). People undertook a 26-week trial, and 26-week extension.

8.44.1. Mean HbA1c decreased from baseline by 0.7% (IDegAsp+IAsp) and 0.6% (IDet+IAsp), achieving 60 or 61 mmol/mol (7.6% or 7.7%, respectively), at Week 52.

8.44.2. The mean total daily insulin dose was lower with IDegAsp+IAsp than with IDet+IAsp (ratio: 0.87; 95% CI 0.79–0.95; $P = 0.0026$). Overall confirmed hypoglycaemia rate was 31.8 episodes/ PYE with IDegAsp+Asp and 36.7 episodes/PYE with IDet+IAsp.

8.44.3. The rate of nocturnal confirmed hypoglycaemia was significantly lower with IDegAsp+Asp than with IDet+IAsp (3.1 vs. 5.4 episodes/PYE, respectively; $P < 0.05$).

8.44.4. Adverse event rates were comparable between groups (IDegAsp+IAsp (73.8%; n = 267/362) and IDet+IAsp (70.6%; n = 127/180) reported treatment-emergent adverse events, the majority of which were mild or moderate in severity).

8.45. The Committee considered the following studies: Kadowaki et al. J Diabetes Investig. 2016;7:711-7, Mathieu et al. J Clin Endocrinol Metab. 2013;98:1154-62, Meneghini et al. Diabetes Care. 2013;36:858-64, which reported that dosing intervals could be variable in those with type 1 or type 2 diabetes, without unduly affecting the risk of hyper or hypoglycaemia.

8.46. The Committee also considered the following studies:

- Taneda et al. J Diabetes, 2017;9:243-47
- Brunner et al. Drugs Aging. 2015;32:583-90
- Biester et al. Pediatr Diabetes. 2016;17:642-9
- Battelino et al. Pediatr Diabetes. 2018;19:1263-70
- Heise et al. Diabetes Obes Metab. 2015;17:659-64
- Onashi et al. J Diabetes Investig. 2017;8:210-7
- Niskanen et al. Eur J Endocrinol. 2012;167:287-94
- Hussanein et al. Diabetes Res Clin Pract. 2018;135:218-26
- Cho et al. Diabetes Metab J. 2020;44:532-41
- Kawaguchi et al. J Diabetes Investig. 2019;10:1527-36
- Shimoda et al. Endocr J. 2019;66:745-52.
- Kumar et al. PLoS One. 2016;11:e0163350.
- Onishi et al. Diabetes Obes Metab. 2013;15:826-32
- Fulcher et al. Adv Ther. 2022;39: 3735-48
- Haluzik et al. Diabetes Obes Metab. 2018; 20:1585-92
- Long et al. Endocr J. 2022;69:959-69

8.47. The Committee noted that some people with type 1 diabetes prefer to undertake multiple daily injections, even if they have access to an insulin pump. The Committee noted that some people with type 1 diabetes, who require twice daily glargine to achieve good glycaemic control, are likely to want to switch to once-a-day insulin degludec as their basal insulin. The Committee noted that some people may not want degludec combined with a fixed ratio of insulin aspart (IDegAsp) and may want to use degludec (IDeg) as monotherapy for basal insulin delivery.

Suitability

8.48. The Committee noted that protamine formulations of premixed insulin require resuspension before administering and considered the solution formulation of insulin degludec/insulin aspart to be of benefit, removing the risks of inaccurate dosing from insufficient mixing of the suspension.

8.49. The Committee considered that insulin degludec/insulin aspart would be of use to those who have non-modifiable, unpredictable variation in the timing of insulin administration, including those who are reliant on community nurses or others for administration.

8.50. The Committee noted that insulin degludec/insulin aspart would be of particular benefit to those who are fasting (eg in relation to Ramadan), and in people with high carbohydrate-based diets, or who have frequent hypoglycaemic events. In addition, the Committee considered it would be beneficial to those who struggle to administer the number of injections required, including young adults who may rely on school nurses to administer their insulin injections.

8.51. The Committee considered that those that progress with type two diabetes from one injection to two when undertaking a basal insulin regime may get the most benefit from insulin degludec/insulin aspart, as would others experiencing difficulty managing multiple daily injections.

8.52. The Committee noted the Kirkgöz et al. J Clin Res Pediatr Endocrinol. 2022 3;14:10-6 study of 50 people with type 1 diabetes, where the disease was poorly controlled on basal-bolus insulin regimes, who were treated with IDegAsp. One year after swapping treatment, 38 people remained on IDegAsp, whereas 12 people had opted to resume their original treatments. In those who continued on IDegAsp, HbA1c levels did not change, but the number of self-reported mild-moderate hypoglycemic episodes decreased significantly ($p<0.05$). In the year before switching to IDegAsp, 11 diabetic ketoacidosis attacks in 9 people were observed, whereas this decreased to 4 attacks in 4 people after one year of IDegAsp therapy ($p=0.06$).

8.53. The Committee noted that multiple insulin products are presented in a flexpen style design, and therefore confusion between insulin products may occur.

Cost and savings

8.54. The Committee noted that less insulin may be required in comparison to NovoMix, as the evidence indicated was a lower unit dose required with insulin degludec/insulin aspart.

8.55. The Committee noted that a reduced number of injections was required, making it easier for the person with diabetes to control their insulin levels with the potential for less hypoglycaemic events to occur. This may reduce the costs associated with the management of hypoglycaemia.

Funding criteria

8.56. Insulin products are funded without restrictions.

8.57. The Committee noted that their interest in a future application for insulin degludec (IDeg) as a monotherapy.

Summary for assessment

8.58. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for insulin degludec/insulin aspart if it were to be funded in New Zealand for diabetes. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Type 1 diabetes (10%)	Type 2 diabetes (90%)
Intervention	Insulin degludec and insulin aspart	Insulin degludec and insulin aspart
Comparator(s) (NZ context)	Insulin glargine	Insulin glargine (86.7%) OR Insulin aspart with insulin aspart protamine (13.3%)
Outcome(s)	• **Increased rate of hypoglycaemic events compared to insulin glargine** (Kumar et al. Diabet Med. 2017;34:180-8) • Non-inferior HbA1c reduction compared to insulin glargine	• **Increased rate of hypoglycaemic events compared to insulin glargine** (Kumar et al. Diabet Med. 2017;34:180-8) • Similar rate of hypoglycaemic events when compared to insulin aspart with insulin aspart protamine • Non-inferior HbA1c reduction compared to insulin glargine and to insulin aspart with insulin aspart protamine

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

9. Diabetes Technology Request for Proposals (RFP) – Insulin Pumps and Continuous Glucose Monitors (CGMs)

9.1. The Committee noted that Pharmac was planning on running a commercial process for the supply of insulin pumps, consumables and CGMs for people with type 1 or pancreatogenic diabetes mellitus (hereafter known collectively referred to as type 1 diabetes). The Committee noted that Pharmac staff were seeking clinical advice from the Committee about:

9.1.1. The technical specifications of insulin pumps and CGMs essential for clinical management.

9.1.2. Eligibility criteria for insulin pumps, consumables and CGMs.

9.1.3. Implementation activities that would be required to support people on insulin pumps, healthcare professionals and the health sector should a brand change result.

9.1.4. Implementation activities that would be required to support funding of CGMs and the listing of CGMs, noting that CGMs are not currently funded.

9.2. The Committee noted that CGMs can be used as a stand-alone device to monitor blood glucose levels or paired with insulin pumps via an algorithm to create a "hybrid closed-loop" or "automated insulin delivery" system that guides insulin delivery.

Funding of CGMs and hybrid closed loop systems used with insulin pumps

9.3. The Committee noted it had previously recommended that the Abbott Freestyle Libre flash glucose monitoring (FGM) system be funded with high priority. However, the Committee also noted that the Freestyle Libre system has since been largely superseded by the Freestyle Libre 2 intermittently scanned-CGM (is-CGM) system which has alarm functionality and continuously monitors interstitial glucose, but still requires the user to scan to see their glucose reading, trend arrow, and 8-hour history. The Committee considered that other low-cost CGM options have also become available. The Committee considered that in light of these developments there was no clinical need to include flash glucose monitoring as part of the commercial process, but that it was important to consider the advantages and disadvantages of both is-CGM and real-time CGM (rt-CGM) options.

9.4. The Committee considered that, in general, all people with type 1 diabetes would benefit from using a CGM device, and that for many patients the available CGMs would provide similar health benefits.

9.5. The Committee considered that many people would substantially benefit from a standalone CGM option and that an option without the capacity to pair with an insulin pump would meet the needs of some of those with type 1 diabetes, acknowledging that insulin pumps were not acceptable to, or appropriate for, some individuals. The Committee considered that there would be a group of people with more complex uncontrolled hyperglycaemia, recurrent diabetic ketoacidosis (DKA) or unexplainable hypoglycaemia who would substantially benefit from hybrid-closed loop therapy and would require a CGM that can pair with a pump. The Committee noted that many of these patients do not meet the current insulin pump criteria.

9.6. The Committee considered that there were other groups who would benefit from access to CGM such as people with gestational diabetes, however, noted that no funding application had been received for use in this setting. Members considered that there is an unmet need for the short-term use of CGM in the hospital setting where patients are on intensive insulin therapy (e.g in the setting of post-organ transplant, oncology, or intensive care).

9.7. The Committee considered that Māori and Pacific people eligible for insulin pumps are not accessing them at the same rate as people of New Zealand European ethnicity, and that access to standalone CGM would be important for Māori and Pacific people who are managing their type 1 diabetes with multiple daily injection (MDI) insulin.

9.8. As such, the Committee considered it would be appropriate to fund one standalone CGM device provided it was funded alongside at least one CGM device capable of hybrid closed-loop interoperability. The Committee considered a standalone CGM option to be appropriate as not everyone with type 1 diabetes would want to use an insulin pump but would still benefit from a CGM. The Committee considered that standalone CGM devices may be less expensive than CGM devices with hybrid closed-loop interoperability, but would still provide additional health benefits for many people with type 1 diabetes.

9.9. The Committee considered that while there may be an increase in demand for insulin pumps if CGMs were to be listed, that there is also a group of people who would be unlikely to want to use hybrid closed-loop systems. The Committee considered that most children would utilise a hybrid closed-loop system, but considered many adults eligible for insulin pumps would choose not to use a hybrid closed-loop system, preferring to use a standalone CGM. The Committee identified the following groups who may prefer to use a stand-alone CGM device over a hybrid closed loop system:

9.9.1. people living with diabetes for whom having an insulin pump attached to their bodies may not be suitable or desirable, for example those living a physically active lifestyle and workers in hot environments.

9.9.2. people living with diabetes who are doing well managing their insulin dosing themselves through MDI and who would prefer to maintain this process rather than shift to an electronically managed system

9.9.3. a small number of people currently accessing insulin pumps who may switch back to MDI if they have access to CGM.

9.9.4. other people who would find an insulin pump invasive, inconvenient to manage, or uncomfortable.

9.10. The Committee considered that some people may become motivated to use a hybrid closed-loop system following the successful trial of a CGM.

9.11. The Committee noted that some suppliers have a range of CGM devices. The Committee discussed the implications of Pharmac contracting with suppliers (for their portfolio of CGM devices) rather than for the individual products themselves which could result in more than two CGM devices funded.

9.11.1. The Committee considered there was no need for an upper limit to the number of CGM devices that could be funded under this scenario, and considered that many clinicians would up-skill as new technologies become available, but that appropriate resourcing would further enable this. The Committee acknowledged that there would likely be a degree of prescribing based on product or brand familiarity.

9.11.2. The Committee considered that resourcing levels may differ significantly across clinics and that staff in more well-resourced clinics would likely be able to dedicate more resource to upskilling and education.

9.11.3. The Committee considered that some people would decide to privately fund CGMs which are not publicly funded and that clinicians would still need to be familiar with these products.

9.12. The Committee considered that clinician familiarity and behaviour is likely to be influenced by the level of onboarding and wraparound support provided by a supplier. As clinicians are increasingly time-pressured, any onboarding and wraparound support that can be provided by a supplier would free up clinician time and resource. The Committee considered that if Pharmac were to fund two suppliers of CGMs, that suppliers would be competing for market share and would be highly motivated to provide strong wraparound support. The Committee considered that suppliers should also provide clinician training and that this training needs to be flexible i.e. options for in-person or online training.

9.13. The Committee considered specific patient populations that need consideration in a commercial process for CGM and insulin pumps.

9.13.1. The Committee considered that the needs of people with visual impairment would need to be considered when evaluating the suitability of insulin pumps and CGMs. The Committee noted that some CGMs have the ability to be voice activated via the operating system. The Committee considered Blind Low Vision NZ would be able to provide more information on the needs of people with visual impairment.

9.13.2. The Committee considered that smaller children require different basal insulin dosing increments than adults, and this needed to be considered when evaluating suitability of insulin pumps and CGMs

9.13.3. The Committee considered that people with disabilities may need additional support systems beyond CGMs, relative to the type and extent of their disability.

9.14. The Committee considered that if there were two brands of insulin pumps and two suppliers of CGMs funded then an Alternative Brand Allowance (ABA) of 5% would likely be sufficient for both insulin pumps and CGMs. The Committee considered that while the products do differ in design, the health benefits are relatively similar across the currently available products. The Committee considered that a waiver process for those people needing an alternative brand of insulin pump or CGM, may provide greater flexibility than strict pre-defined exception criteria, and would allow clinicians to identify these exceptions as they arise.

9.15. The Committee noted that Pharmac has not received a funding application for CGMs for type 2 diabetes. The Committee considered that if CGMs were funded in the future for people with type 2 diabetes they would use CGMs differently to people with type 1 diabetes. In type 2 diabetes, short-term use of CGMs would be useful to monitor day-to-day trends in glycaemic control and glycaemic excursions, to help inform long term adjustments in behaviour and insulin therapy. The Committee considered that up to 10% of people with type 2 diabetes taking insulin would benefit from a hybrid closed loop system, this group being functionally similar to people with type 1 diabetes, at least from a disease management point of view.

Technical specifications required for insulin pumps

9.16. The Committee noted that insulin pumps and CGMs are publicly funded for type 1 diabetes in other jurisdictions including the United Kingdom and Australia. The Committee suggested Pharmac may like to investigate what the minimum technical and functional specifications required are internationally.

9.17. The Committee considered that children and adults of low body weight would likely require different dosing increments than other adults, and this needed to be considered when evaluating the suitability of insulin pumps. Members considered that the minimum daily insulin dose of certain pumps would not be appropriate for use in smaller children.

9.18. The Committee noted that ‘tubeless’ or patch insulin pumps are available in Australia. The Committee considered that ‘tubeless’ insulin pumps could be appropriate to include as part of the commercial process, however if a tubeless insulin pump was to be funded as part of the commercial process there would still be a need for a tubed insulin pump. The Committee considered it did not need to review separate funding applications for insulin pumps that it has not previously assessed and that an internal evaluation process would be appropriate for these devices.

9.19. The committee noted it was important that the companies that are contracted with have an active Research and Development pipeline to ensure that the funded products can be updated as technology evolves.

Insulin pump consumable considerations

9.20. The Committee noted that a maximum of 13 packs of insulin pump infusion sets are currently funded per 12 month period. The Committee considered the 13-pack limit was insufficient for people requiring higher doses of insulin, and that this had equity implications for some people who on average require higher doses of insulin for clinical reasons. The Committee noted that current practice is to

manually top-up the infusion set but this is impractical for many people. The Committee also considered that the 13-pack limit was insufficient for those who required more regular insertion site changes (ie for those with site allergies or with scar tissue formation). The Committee recommended linking the maximum number of funded consumables to a patient's daily insulin dose. The Committee considered a maximum of up to 36 sets per 12 months could be endorsed for those who require > 100 units of insulin per day or require frequent site changes.

9.21. The Committee noted anecdotal evidence that some people access funded insulin pump consumables and share these with people who are not eligible for funded consumables. An example provided was that some people ineligible for funded insulin pumps may acquire an out of warranty "hand-me-down" insulin pump and then share funded consumables with someone who is eligible for funded consumables. This results in both people using their consumables past their recommended shelf-life, which may subsequently result in poorer glycaemic control.

9.22. The Committee also noted anecdotal evidence that some people use consumables past their recommended in-use life due to the inconvenience of regularly replacing consumables.

Technical specification requirements for Continuous Glucose Monitors

9.23. The Committee considered the following technical specifications would need to be considered when evaluating bids in a commercial process: Accuracy, sensor life, on-set and off-set of sensors ('wake up' times), transmitter warranty periods, availability of a reader device, calibration requirements, size and ease of use of applicator, connectivity and data sharing, hypoglycaemic and hyperglycaemic alerts, and closed loop functionality. In addition to technical specifications of CGMs the Committee considered it would be important to consider each supplier's plans for future development and upgrades, and for suppliers to provide the details of any software licencing agreements. The Committee considered that suppliers should provide any relevant literature and evidence to support the technical specifications of each device. However, the Committee considered that newer products may not have as much published supporting evidence compared to older products.

9.24. The Committee considered that accuracy/Mean Absolute Relative Difference (MARD) requirements differ depending on how the CGM device is being used. Members considered that CGM accuracy is more important when it is being used in an advanced hybrid-closed loop setting. The Committee also considered it important for CGM devices to have high accuracy in the hypoglycaemic and hyperglycaemic ranges, particularly to enable the accurate detection of incipient hypoglycaemia.

9.25. The Committee noted that some CGM devices have a standalone reader device while some CGMs must be used with a smartphone. The Committee considered that if Pharmac were to fund more than one CGM device, at least one must come with a standalone reader device that does not require a smartphone to operate. The Committee considered there could be equity issues with CGMs that require smartphones. Some of the issues highlighted by the Committee included some people using a shared phone (e.g. a family phone), CGMs not being compatible with all smartphones, not all children owning personal phones, and potential compatibility issues due to software or operating system updates.

9.26. The Committee noted that the accuracy of CGM sensors may wane over time and that the risk of contact dermatitis increases with longer life sensors. Members considered that some CGM sensors have evidence for reliable readings when

attached to a variety of body sites, which may help manage the risk of skin reactions. The Committee considered that evaluation of sensors and sensor life should balance the convenience of needing to replace the sensor less frequently against the increased risk of dermatitis and potential reduced accuracy over time. The Committee considered sensor lifespan to be less important than accuracy.

9.27. The Committee noted that the onset and offset periods of sensors varies between brands. The Committee considered a shorter CGM sensor "warm up" period to be beneficial, as patients have limited access to their glycaemic information during this time. The Committee noted that warm up periods are constantly improving (ie reducing) as suppliers innovate.

9.28. The Committee noted that diabetes technology is developing at a rapid pace, and recommended that Pharmac include a requirement for suppliers to provide an overview of their product/R&D pipeline in their response to any procurement process.

9.29. The Committee noted that some newer devices do not require fingerprick testing for calibration. The Committee considered this a significant suitability advantage over devices that require calibration.

9.30. The Committee considered that while it did not need to review separate funding applications for CGM devices prior to the release of any procurement activity (or once the activity had closed), a clinical evaluation committee would need to assess the respective product bids. The Committee considered that there were no known minimum technical specifications that should exclude available products from consideration.

9.31. The Committee noted that there is a significant plastics/electronics waste burden with single-use sensor applicators. The Committee considered reusable applicators would have environmental sustainability advantages.

9.32. The Committee noted that there are currently four different dosing algorithms available in New Zealand and considered it likely there were differences in performance between them. While the Committee acknowledged that there were very few head-to-head trials comparing the performance of each algorithm or closed-loop system, the Committee considered it would be most relevant to consider the relative performance against current alternatives, albeit indirectly. The Committee also considered that while it would be easy to compare functionality within a supplier's portfolio, it would be more challenging to compare the functionality of algorithms and products across different suppliers.

9.33. The Committee noted that different algorithms are indicated for different age ranges and minimum daily insulin doses, and this needed to be considered when evaluating the suitability of algorithms.

9.34. With regards to connectivity and data sharing, the Committee considered it would be important to ask suppliers for information as part of the commercial process to understand what cloud-based computing on-demand network platform the supplier uses. The Committee considered it is important to consider where the data is stored. In addition, the Committee considered that it would be helpful if suppliers provided clinicians with written information that they could provide their patients to explain where the data goes, how it is used and how it is kept private.

9.35. The Committee considered that evaluation of bids as a result of a commercial process for CGMs, and insulin pumps should include clinical expert and consumer groups. The Committee considered that if the devices were too technical to be evaluated by clinical experts, then a specialised technical group may need to be consulted. The Committee noted that many diabetes clinicians were familiar with

the majority of products currently available in New Zealand.

Insulin pump eligibility criteria

9.36. The Committee noted Pharmac staff were seeking clinical advice to simplify the current eligibility criteria for insulin pumps as part of the commercial process for insulin pumps, consumables and CGMs.

9.37. The Committee considered the following Special Authority criteria would be appropriate, and would still target funding to the group intended:

> **Initial application** (type 1 diabetes). From any relevant practitioner. Approvals valid for 2 years for applications meeting the following criteria:
>
> All of the following:
>
> 1. Patient has type I or pancreatogenic* diabetes mellitus; and
> 2. Patient has been evaluated by a diabetes multidisciplinary team for their suitability for insulin pump therapy; and
> 3. Either;
>   - 3.1 Has adhered to an intensive MDI regimen using analogue insulins for at least three months but still has;
>   - 3.1.1 severe unexplained recurrent nocturnal hypoglycaemia; or
>   - 3.1.2 one or more severe unexplained hypoglycaemic events requiring assistance; or
>   - 3.1.3 chronically raised HbA1c despite optimal MDI therapy; or
>   - 3.2 in the opinion of the treating specialist a trial with an MDI regimen would be unsuitable and clinically inappropriate.
>
> * This includes permanent neonatal diabetes or patients with insulin deficiency secondary to cystic-fibrosis or pancreatectomy.
>
> **Renewal** – (type 1 diabetes) any relevant practitioner. Approvals valid for 2 years for applications meeting the following criteria:
>
> Patient is continuing to derive benefit according to the treatment plan agreed at induction and objective evidence of current glycaemic control.

9.38. The Committee considered that insulin pumps need to be initiated in secondary care but that CGMs could be initiated by any practitioner with the relevant expertise in the management of type 1 diabetes. However, the Committee considered that extra funding and resource may be required for CGM onboarding to occur in primary care, as this process would likely need longer than a standard 15-minute consultation.

9.39. The Committee considered that it was necessary for insulin pump onboarding to take place within diabetes multidisciplinary teams, given the level of patient education, engagement and partnering required to use these devices safely and effectively.

9.40. The Committee considered that renewal criteria were required to ensure the target group are continuing to derive a health benefit from the pump beyond that of MDI alone. However, the Committee considered that amending the current glycaemic bands in the renewal criteria could improve equity of access. The Committee considered that the renewal criteria should include reference to an objective measurement of improvement in glycaemic control eg laboratory confirmed improvement in HbA1c or confirmed improvement in the proportion of total time within the recommended glycaemic range.

9.41. The Committee considered a 2-year initial approval and renewal timeframe to be appropriate.

Transition periods and support should there be a brand change of insulin pump(s) resulting from the commercial process for insulin pumps and CGM

9.42. The Committee considered that if there was to be a brand change to insulin pump(s) resulting from the commercial process, there would need to be a long transition period to support some people and the health sector to manage this. The Committee considered that while some people may be able to transition quickly without difficulty, others may have a psychological affinity with their pumps and the change could be difficult. Members considered some of those people experiencing the change as difficult could need a transition period of up to 2 years.

9.43. The Committee considered there would need to be supplier provided implementation support in the form of training and education and ongoing support for both people with diabetes and healthcare professionals if there was to be a change.

9.44. The Committee considered that the evaluation of proposals should consider the proposed implementation support specifically for Māori and Pacific peoples. The Committee considered that implementation support would require more than simply providing written materials in Te Reo Māori or Pacific languages, which may not necessarily be appropriate for all Māori and Pacific people. Of more importance is the format through which suppliers intend to engage with Māori and Pacific populations, for example engaging with communities, having community-based face-to-face training or online training materials may be more appropriate for some groups compared to eg passively printing a written leaflet.