Record of the Diabetes Subcommittee of PTAC Meeting held on 24 September 2021

Diabetes Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

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

The Diabetes Subcommittee 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.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

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

PTAC Subcommittees 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 PTAC Subcommittees, 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

Sean Hana (Chair)
Bruce King
Diana McNeill
Esko Wiltshire
Helen Lunt
Kate Smallman
Karen Mackenzie
Nic Crook
Tim Stokes
Rinki Murphy

Apologies:
Elizabeth Dennett

2. The role of PTAC Subcommittees and records of meetings

2.1. This meeting record of the Diabetes Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

2.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

2.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

2.4. The Diabetes Subcommittee is a Subcommittee of PTAC. The Diabetes Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Diabetes Subcommittee and other PTAC Subcommittees 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 Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

PHARMAC considers the recommendations provided by both the Diabetes Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for Diabetes.

3. Declared interests

3.1. The Subcommittee reported the following conflicts of interest:

3.1.1. A member declared a family health related conflict. The chair determined that the member could participate in discussions but not vote.

4. SGLT-2 Inhibitors & Ketone Monitoring

The Subcommittee were asked to provide advice on funding ketone monitoring for high-risk patients on SGLT-2 inhibitors.

4.1. The Subcommittee noted that from 1 February 2021 empagliflozin was funded for people with type 2 diabetes mellitus subject to eligibility criteria. The Subcommittee noted that since being listed there had been reported cases of euglycemic diabetic ketoacidosis (DKA).

4.2. The Subcommittee noted that euglycemic DKA is a rare but serious complication associated with the use of SGLT-2 inhibitors, whereby ketone accumulation in the blood occurs alongside uncharacteristically mild-to-moderate glucose elevations.

4.3. The Subcommittee noted that DKA typically presents with non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, or unusual fatigue or sleepiness, regardless of blood glucose level.

4.4. The Subcommittee noted that dual blood glucose and blood ketone monitors are funded by endorsement for those who meet the current insulin pump criteria or for those with metabolic disease or epilepsy under the care of a paediatrician, neurologist, or metabolic specialist. The Subcommittee considered that the current requirement for endorsement was challenging as it requires practitioners to annotate prescriptions with one of the five requisite criteria.

4.5. The Subcommittee considered that the monitoring of ketones should be considered in situations where DKA is a risk, such as fasting prior to surgery, or in certain paediatric and adolescent populations, but considered that it was not standard practice to monitor blood ketones in adults with uncomplicated type 2 diabetes.

4.6. The Subcommittee noted that if DKA is suspected it is recommended that patients cease treatment with SGLT-2 inhibitors and considered that as clinicians get more experienced in prescribing SGLT-2 inhibitors, the demand for ketone testing will subside.

4.7. The Subcommittee considered that it would be useful for members to engage with key stakeholder groups, including the anaesthetic and surgical communities, to better define high-risk patient groups prior to the next Diabetes Subcommittee meeting.

4.8. The Subcommittee considered that the Pharmac could make the current endorsement simpler by restricting funding to specialists working within their vocational scope. Furthermore, the Subcommittee considered that Pharmac could review the limit of ten strips available on a practitioner supply order (PSO) alongside any changes to the endorsement criteria to reduce administrative burden.

5. Dexcom G6 Continuous Glucose Monitoring – Type I Diabetes

Interests

5.1. The Subcommittee reported no additional conflicts of interest with regard to this agenda item.

Application

5.2. The Subcommittee considered a supplier application from New Zealand Medical and Scientific Limited for the use of Dexcom G6 continuous glucose monitoring (CGM) system for people with type 1 diabetes mellitus.

Recommendation

5.3. The Subcommittee **recommended** that the Dexcom G6 CGM be listed with a high priority within the context of type 1 diabetes subject to the following Special Authority criteria:

> **Initial application**
> Applications only from Registered Medical Practitioners or Nurse Practitioners. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1.0 Patient has permanent neonatal diabetes, or
> 2.0 Patient is aged ≥2 years; and
> 3.0 Either:
> 3.1 Patient has type 1 diabetes, or
> 3.2 Patient has undergone a pancreatectomy, or
> 3.3 Patient has insulin-requiring diabetes secondary to cystic fibrosis.
>
> **Renewal application**
> Applications only from Registered Medical Practitioners or Nurse Practitioners. Approvals valid for 24 months for applications meeting the following criteria:
> 1. Patient is continuing to derive benefit from RT-CGM by achieving mutually (clinician and patient) agreed goals

5.4. In making this recommendation, the Subcommittee noted:

- the health needs of people with type 1 diabetes, their families/whānau and wider society
- the evidence of health benefit associated with continuous glucose monitoring, particularly when paired with insulin pump therapy
- the suitability benefits associated with continuous glucose monitoring

5.5. In making this recommendation the Subcommittee also noted that the Dexcom G6 is both interoperable with several different insulin pump options and does not require regular calibration with finger prick testing.

Discussion

General comments regarding type 1 diabetes

5.6. The Subcommittee noted that type 1 diabetes is a chronic disease resulting from the autoimmune destruction of pancreatic β-cells resulting in insulin deficiency. The Subcommittee noted that individuals with type 1 diabetes use exogenous insulin to manage blood glucose levels but that maintaining a normal range requires a significant mental energy and can lead to diabetes-related fatigue. The Subcommittee noted that sustained fatigue can lead to burnout and poor glycaemic control.

5.7. The Subcommittee noted a recent epidemiological study conducted by Chepulis et al. (2021) which recently estimated that the population prevalence of type 1 diabetes to be approximately 0.4% of the population, equating to 20,000 New Zealanders. The Subcommittee noted that another study conducted by Wheeler et al. (2019) which, utilising a hospital admissions and dispensing data, estimated the prevalence of type 1 diabetes to be 17,338 people between 1 September 2012 and 31 December 2016.

5.8. The Subcommittee noted that the current standard of care for glucose monitoring is self-monitoring via a finger-prick blood test with or without the addition of continuous subcutaneous insulin infusion (CSII) using an insulin pump. The Subcommittee noted that patients with good glycaemic control are typically testing on average between four and ten times per day and considered that adherence to this regimen could be challenging especially for children and young adults, as it involves maintaining a careful balance of insulin dosing, dietary intake, and exercise. The Subcommittee noted that many patients seldom test their blood glucose, but rather approximate their bolus insulin dosing to food intake and rely on a minimum viable dose of basal insulin.

5.9. The Subcommittee considered that type 1 diabetes has a significant negative impact on quality of life for affected individuals, particularly regarding physical functioning and wellbeing. The Subcommittee noted that glycaemic variability and sustained poor glycaemic control can lead to severe microvascular and macrovascular complications, as well as diabetic ketoacidosis and death.

5.10. The Subcommittee noted that the perpetual fear of hyperglycaemia or hypoglycaemia, as well as the fear of long-term complications, can result in significant stress and anxiety. Furthermore, the Subcommittee noted that there is also a significant impact on the family and caregivers of individuals with type 1 diabetes.

5.11. The Subcommittee noted that while the incidence of type 1 diabetes is lower in Māori and Pacific peoples, they are disproportionately represented in hospital admissions data for diabetic ketoacidosis and suffer significantly poorer outcomes than other patient populations. The Subcommittee noted that a study by Carter et al. (2008) reported that lower SES and ethnicity were independent predictors of poor glycaemic control in children with type 1 diabetes.

General Comments Regarding CGM and FGM

5.12. The Subcommittee noted that diagnostic blood glucose test meters and strips are funded for patients meeting certain eligibility criteria, including individuals receiving insulin and that there are currently no flash or continuous glucose monitoring (CGM) systems funded for use within New Zealand. The Subcommittee noted that it had previously recommended the Freestyle Libre flash glucose monitoring (FGM) system for funding with a high priority. The Subcommittee noted that FGM systems permits manual sensor augmented multiple daily insulin (MDI) dosing with better data, but not the advantage of advanced features of insulin pump therapy.

5.13. The Subcommittee noted that CGM systems utilise sensor electrodes inserted into the subcutaneous tissue (usually on the abdomen), to measure glucose in the interstitial fluid, which is then converted into an electronic signal and transmitted via a low energy Bluetooth signal (range in the air about 6 meters) to either a reader or smart device where it is displayed for the user as a glucose reading.

5.14. The Subcommittee noted that there are functional distinctions between CGM and FGM, namely that CGM systems include a transmitter that automatically transmits a continuous stream of real-time numerical and graphical information about the current glucose level and velocity of change to the user's optional receiver or smartphone.

5.15. The Subcommittee noted that while current FGM systems do provide glucose level trend arrows to encourage closer monitoring or intervention, they tend to be user-initiated and typically require the sensor to be manually scanned with a reader device. The Subcommittee considered that the major limitation of FGM systems is that they not designed to be integrated with insulin pumps or provide alarm features for either predicted nor actual hypoglycaemia.

5.16. The Subcommittee noted that CGM systems can be used as a stand-alone monitoring device to guide insulin delivery or paired with an insulin pump as an integrated pump system with advanced features such as predictive low glucose suspend and bolus autocorrections. The Subcommittee considered integrated pump therapy to be a significant improvement from the status quo for people with type 1 diabetes, which is either capillary glucose informed MDI or capillary glucose informed pump therapy.

5.17. The Subcommittee noted that integrated pump systems vary significantly in their functionality based on the software used to pair the devices. The Subcommittee considered there to be the following classes of integrated pump systems:

- Sensor-augmented pump (SAP) therapy: where there is little or no interoperability between the pump and the CGM system and the user must make data-informed decisions around basal settings and bolus dose calculations.

- Hybrid closed-loop (HCL) systems: where an algorithm modulates basal insulin delivery with predictive-low glucose suspend of insulin delivery but does not give automated boluses.

- Advanced hybrid-closed loop (AHCL) systems: where an algorithm enables automated correction boluses, a meal detection module can let the system deliver more aggressive automated correction boluses and intensification of basal insulin delivery to consistently target near normal glycaemia.

5.18. The Subcommittee noted that CGM systems can differ substantially in their accuracy, build-quality, calibration requirements, and closed-loop functionality. The Subcommittee considered that the field of glucose monitoring technologies was evolving rapidly and noted that funding applications for the Dexcom and Guardian CGM systems were the first to be referred to the Subcommittee for clinical advice.

5.19. The Subcommittee considered that CGM systems are likely to improve the time spent in the target glycaemic range (TIR), reduce the time spent in hypoglycaemia, and reduce the number of hypoglycaemic events requiring medical attention when used with or without insulin pump therapy. However, the Subcommittee considered that the major benefits were likely to accrue when paired with an insulin pump. The Subcommittee noted that this was particularly true of when the CGM is integrated with an insulin pump with advanced features such as sensor informed correction boluses and predictive low glucose suspend.

5.20. The Subcommittee considered that these technologies would likely benefit all people with difficult to control diabetes with the evidence strongest for the use in the type 1 diabetes setting. The Subcommittee considered that patients with diabetes secondary to cystic fibrosis and patients who have undergone a pancreatectomy, should be considered within the same grouping of 'people with diabetes treated with intensive insulin therapy.'

5.21. While the Subcommittee noted that there were benefits associated with CGM systems in place of finger-prick testing, the Subcommittee considered that these benefits may wane overtime, with some patients suffering from 'user fatigue' associated with the constant stream of information. The Subcommittee considered that this was less likely to be the case if used in a hybrid closed loop system with an insulin pump. The Subcommittee considered that FGM informed MDI may be more suitable in people with type 1 diabetes who are not eligible for insulin pump therapy. The Subcommittee also noted that FGM sensors can be used for up to 14 days of use, almost twice the duration of many CGM systems.

5.22. The Subcommittee noted that both FGM and CGM systems can be used on a temporary basis or intermittent basis for patients initiating multiple daily injection (MDI) regimens to enable insulin dose-titration. The Subcommittee noted that CGM data can also inform decisions around driving safety, particularly among those with hypoglycaemic unawareness.

5.23. The Subcommittee considered that CGM systems were most beneficial to patients with type 1 diabetes when paired with an insulin pump, but that there are people with type 1 diabetes who would benefit from these technologies who do not meet the current pump SA eligibility criteria. The Subcommittee considered that the pump criteria should be reviewed to identify patient subpopulations that would most benefit from the paired technologies but that there was a clear unmet health need in type 1 diabetes patients with severe unexplained hypoglycaemia and/or recurrent DKA in the first instance.

5.24. The Subcommittee noted that there were a number of equity considerations relating to the funding of CGM particularly regarding equity of access to the digital technologies (i.e. smart phones) required to utilise some CGM systems. The Subcommittee noted variable resourcing across DHBs to implement education and initiation of CGM technologies.

5.25. The Subcommittee noted that CGM systems are widely available internationally and is subsidised in Australia (under the Australian National Diabetes Services Scheme) and in England by the NHS. The Subcommittee noted that there is a large private market in New Zealand for these technologies.

5.26. The Subcommittee considered that it should be a priority to list at least one CGM system on the Pharmaceutical Schedule and that the recommendations on whether to fund or decline particular products should be noted in within this context.

Dexcom G6 CGM

5.27. The Subcommittee noted that the Dexcom G6 CGM system consists of an indwelling sensor and applicator, a transmitter, and either a display device or a smart phone. The Subcommittee noted that the sensor attaches to the skin with its adhesive patch and is replaced every 10 days.

5.28. The Subcommittee noted that the Dexcom G6 CGM transmitter wirelessly sends glucose information to a receiver or smart device running the Dexcom G6 CGM Application. The Subcommittee noted that the transmitter has a battery life of 90 days, so can be reused for approximately nine sensor sessions.

5.29. The Subcommittee noted that the Dexcom G6 CGM provides an urgent "low soon" alert that lets the user know when their glucose is falling so fast it will drop to ≤ 3.1 mmol/L in less than 20 minutes. The Subcommittee considered that predictive low glucose alerts were effective in reducing frequency, severity, and duration of rebound hypoglycaemia, as well as quality of life and sleep for patients and their family.

5.30. The Subcommittee noted the Dexcom G6 subcutaneous glucose sensor, monitoring system, and software are all registered on the Web Assisted Notification of Devices (WAND) database, which is a mandatory requirement for importers, exporters, and local manufacturers (Glucose Sensor WAND reference: 180612-WAND-6QHVJD, Dexcom Glucose Monitoring System WAND reference: 120726-WAND-6DPSOM, Self-care monitoring web-based application software WAND reference: 170120-WAND-6NH34Y) and that Dexcom CGM devices are registered for the management of diabetes in persons aged two years and older in several other OECD countries.

5.31. The Subcommittee noted that the Dexcom G6 CGM can be paired with a number of insulin pumps, including the Tandem T: slim X2 using proprietary Basal-IQ software, a predictive low-glucose suspend feature that predicts and helps prevent hypoglycaemic events. Furthermore, the Subcommittee noted that soon to be released Control-IQ software would enable greater hybrid closed-loop functionality with automated bolus adjustment, enabling more accurate mealtime dosing with less intensive carbohydrate counting and eliminating the need for finger-prick testing for calibration. The Subcommittee considered that this would significantly decrease the burden of type 1 diabetes management.

5.32. The Subcommittee noted that Dexcom Share allowed data to be shared with third parties including health care professionals, friends, family and whānau. The Subcommittee considered that this could be used to improve the calibration of insulin infusion to the patient's needs, but that there would need to be consideration given to data sovereignty, security, and permission (consent). The Subcommittee

noted that DHBs are required to conduct privacy impact assessments and cloud risk assessments on data sharing applications and that vendors would need to work with DHBs on these assessments.

5.33. The Subcommittee noted that the primary evidence for the use of CGM in people with type 1 diabetes when compared to SMBG is provided by a small number of randomised controlled trials (RCT):

- The Subcommittee noted the DIAMOND trial (Beck et al. JAMA. 2017. 24;317(4):371-8.) an open-label RCT which included 158 adults 25 years and older. The Subcommittee noted that the primary outcome measure, a difference in change in central-laboratory-measured HbA1c level from baseline to 24 weeks, was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4% in the control group (P < .001). The Subcommittee also noted that metrics for time in range, hyperglycaemia, hypoglycaemia, and glycaemic variability favoured the CGM group compared with the control group.

- The Subcommittee noted the GOLD trial, a cross-over RCT which compared the Dexcom G4 Platinum with self-monitoring in adults aged 18 or above with type 1 diabetes treated with MDIs and with an HbA1c of at least 7.5% (Lind et al. JAMA. 2017. 24;317(4):379-87; Ólafsdóttir et al. Diabetes technology & therapeutics. 2018. 1;20(4):274-84.; Ahmadi et al. 2020. 1;43(9):2017-24). The Subcommittee noted that mean HbA1c was 7.92% (63 mmol/mol) during CGM use and 8.35% (68 mmol/mol) during conventional treatment (mean difference, −0.43% [95% CI, −0.57% to −0.29%]; P < .001). The Subcommittee also noted reduction in the time spent in the hypoglycaemic range (particularly at night), and a reduction in hypoglycaemic fear during the CGM phase.

- The Subcommittee noted the WISDM trial, an open-labelled RCT conducted comparing the Dexcom G5 CGM system with self-monitoring of blood glucose in older adults aged between 65-71 years, which reported significant reductions in HbA1c and time spent in a hypoglycaemic range in the CGM arm at follow-up (Pratley et al. 2020. JAMA 16;323(23):2397-406; Carlson et al. Journal of diabetes science and technology. 2021. 15(3):582-92).

- The Subcommittee noted the HypoDE open-labelled RCT conducted across 12 diabetes practices in Germany (Heinemann et al. The Lancet. 2018. 7;391(10128):1367-77). The Subcommittee noted that this trial also compared the Dexcom G5 CGM system with self-monitoring in 149 adults (aged 18 or above). The Subcommittee noted that the primary outcome, the number of hypoglycaemic events measured, was significantly reduced in the unmasked CGM when compared to the masked or self-monitoring group (incidence rate ratio 0·28 [95% CI, 0·20 to 0·39], P <0·0001).

5.34. The Subcommittee also noted the following trials which provided support for the use of CGM in children and young people;

- Thabit et al. Diabetes Care. 2020. 43(10):2537-43
- Laffel et al. JAMA. 2020. 323(23):2388-96
- DiMeglio et al. Diabetic Medicine. 2020. 37(8):1308-15.
- Burckhardt et al. Diabetes Care 2018. 41(12):2641-3.

5.35. The Subcommittee noted two trials comparing CGM with FGM:

- ALERTT-1: a prospective, open-labelled RCT which included 254 adults with type 1 diabetes with previous use with a FGM system to determine whether switching to a CGM system with alert functionality offered improvements in glycaemic control (Visser et al. The Lancet. 2021. 397(10291):2275-2283). The Subcommittee noted that after 6-months the CGM arm had a more favourable time in the target glycaemic range compared with the FGM arm (59·6% vs 51·9%; mean difference 6·85 percentage points [95% CI 4·36–9·34]; P<0·0001).

- IHART-CGM: an open-labelled trial of 40 adults with type 1 diabetes using an MDI regimen which randomised patients into CGM and FGM groups following 2 weeks of blinded CGM (Reddy et al. Diabetic Medicine. 2018. 35(4):483-90). The Subcommittee noted that at the study endpoint the percentage of time spent in the hypoglycaemic range (< 3.3 mmol/l) was 2.4%, and 6.8%, respectively (median between group difference −4.3%, P = 0.006).

5.36. The Subcommittee noted that both trials reported a small but marked improvement in glycaemic control (as measured by time in the target glycaemic range, HbA1c, and hypoglycaemic events) associated with use of CGM use when compared with FGM. The Subcommittee noted that the IHART-CGM extension reported a reduction in the percentage of time spent in the hypoglycaemic range over the 16-week extension (Avari et al. Journal of diabetes science and technology. 2020.14(3):567-74), however, the Subcommittee considered that the extension period was still too short to validate the durability of response.

5.37. The Subcommittee noted that the strongest evidence of benefit in terms of time in range and HbA1c was when the Dexcom G6 was paired with a matching pump and Control IQ in an AHCL system (Brown et al. NEJM. 2019.381:1707-1717). The Subcommittee noted that, compared with SAP therapy, AHCL led to time in range (TIR) improvements of approximately 11 percentage points (95% confidence interval [CI], 9 to 14; P<0.001) after 6 months. The Subcommittee noted that TIR results of around 70% were likely to have a significant impact on the risk of developing diabetes-related microvascular complications.

5.38. The Subcommittee considered that the strength and quality of the evidence for the use of Dexcom G6 was moderate, due to the paucity of controlled trials, the limited duration of the trial periods and the use of different comparator arms. However, the Subcommittee considered that from the evidence that is available, that CGM systems facilitate improved glycaemic control when compared with self-monitoring and that this improvement is more significant when configured with a pump in an AHCL system.

5.39. The Subcommittee considered that interoperability, factory calibration, and high accuracy make the Dexcom G6 a suitable CGM option for people with type 1 diabetes. The Subcommittee recommended that it be funded with a high priority for all people with type 1 diabetes.

5.40. The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for the Dexcom G6 CGM if it were to be funded in New Zealand for people with type 1 diabetes and those with diabetes secondary to cystic fibrosis or pancreatectomy. 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 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	Adults and children above two years of age with any of the following conditions: • Type 1 diabetes • Insulin requiring diabetes secondary to cystic fibrosis • Patient has undergone a pancreatectomy • Permanent neonatal diabetes
Intervention	Dexcom G6 CGM system with or without CSII
Comparator(s) (NZ context)	Patients with Type I Diabetes who use SMBG with or without CSII.
Outcome(s)	The key therapeutic intent of CGM systems is to improve the user's glycaemic control as measured by: • A reduction in hypoglycaemic events • A reduction in HbA1c • Improved time in the target glycaemic range • Reduced time in the hypoglycaemic range • Reduced time in the hyperglycaemic range • Patients and their families QoL metrics With improved glycaemic control, we would expect a reduction in diabetes related microvascular complications over time.
Table definitions: **P**opulation: The target population for the Pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention Pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: 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). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

6. Medtronic Guardian 3 Continuous Glucose Monitoring System –Type I Diabetes

Interests

6.1. The Subcommittee reported no additional conflicts of interest with regard to this agenda item.

Application

6.2. The Subcommittee considered an application from InterMed Medical Limited for the use of the Medtronic Guardian 3 continuous glucose monitoring (CGM) system for people with type 1 diabetes mellitus.

Recommendation

6.3. The Subcommittee **recommended** that Pharmac decline to list the Medtronic Guardian 3 CGM system on the Pharmaceutical Schedule.

6.4. In making this recommendation, the Subcommittee noted that:

6.4.1. The Medtronic Guardian 3 system has been superseded by newer products with greater functionality, such as the Medtronic Guardian 4 CGM or the Dexcom G6 CGM.

6.4.2. A paucity of data to support this particular system.

Discussion

Medtronic Guardian 3 CGM system

6.1. The Subcommittee noted the application for the Medtronic Guardian 3 system for people with type 1 diabetes. The Subcommittee noted that the Guardian 3 system consists of the Guardian Sensor (3) glucose sensor, the Guardian Connect transmitter and the Guardian Connect application (app).

6.2. The Subcommittee noted that the Guardian Link transmitter receives and sends data to the Guardian Connect app through a Bluetooth Smart wireless connection and that the app can be downloaded onto any mobile device with a compatible operating system version.

6.3. The Subcommittee noted that the Guardian Sensors work for up to 7 days and can be placed on a patient's abdomen or on the back of the arm. The Subcommittee noted that the transmitter can be worn for up to 7 days at a time without recharging and have a 12-month lifespan.

6.4. The Subcommittee noted that the Guardian 3 system, can pair with both currently Pharmac-funded Medtronic pumps (the MiniMed 640G and the MiniMed 770G). The Subcommittee noted that when paired with the MiniMed 640 users can utilise a predictive low glucose suspension function, while the MiniMed 770G offers greater closed-loop functionality through automatic basal insulin adjustment.

6.5. The Subcommittee noted that glucose readings are updated every five minutes to the patients pump screen or the user's smart device via the MiniMed application. The Subcommittee noted that CGM alerts notify the individual of high and low glucose values, and graphs and trend arrows show the speed and direction glucose levels are moving. The Subcommittee noted that the CGM system has an in-built hypoglycaemia threshold for alarm which can be adjusted by users.

6.6. The Subcommittee noted the Medtronic Guardian 3 glucose sensor and transmitter are registered on the Web Assisted Notification of Devices (WAND) database, which is a mandatory requirement for importers, exporters, and local

manufacturers (Glucose Sensor WAND reference: 071010-WAND-77484E, Glucose Transmitter WAND reference: 071010-WAND-77U8G8).

6.7. The Subcommittee noted that unlike the Dexcom G6 CGM system, the Medtronic Guardian 3 system requires frequent calibration (up to four times per day) with finger-prick testing for reliable performance. The Subcommittee considers that frequent calibration is a significant driver of patient disengagement.

6.8. The Subcommittee noted the following studies provided by the supplier in the application for funding:

- Bergenstal et al. N Engl J Med. 2013. 18;369(3):224-32
- Charleer et al. J Clin Endocrinol Metab. 2018. 103(3):1224-1232
- Choudhary et al. Diabetes Technol. & Therap. 2016. 18(5):288-291
- Deiss et al. Diabetes Care. 2006;29(12):2730-2
- Ly et al. JAMA. 2013. 310(12):1240-7
- Messer et al. Diabet Med. 2018. 35(4):409-418
- Rickles et al. J Clin Endocrinol Metab. 2018. 103(1):105-114
- Zhong et al. Diabetes Technol Ther. 2016. 18(10):657-663

6.9. The Subcommittee noted the evidence provided by the supplier broadly supports the wider CGM literature in reporting improvements in glycaemic control compared with patient self-monitoring, however, the Subcommittee considered the evidence to be of poor quality overall, namely due to the lack of high-quality clinical trial data.

6.10. The Subcommittee noted that there was significant benefit in providing MiniMed users with a compatible CGM option, however, that this particular CGM system had been superseded by products with greater functionality. As such, the Subcommittee recommended this particular product for decline.

6.11. The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for the Medtronic Guardian 3 CGM if it were to be funded in New Zealand for people with type 1 diabetes and those with diabetes secondary to cystic fibrosis or pancreatectomy. 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 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	Adults and children above two years of age with any of the following conditions: • Type 1 diabetes • Insulin requiring diabetes secondary to cystic fibrosis • Patient has undergone a pancreatectomy

	• Permanent neonatal diabetes
Intervention	Medtronic Guardian 3 CGM system with or without CSII
Comparator(s) (NZ context)	Patients with Type I Diabetes who use SMBG with or without CSII.
Outcome(s)	The key therapeutic intent of CGM systems is to improve the user's glycaemic control as measured by: • A reduction in hypoglycaemic events • A reduction in HbA1c • Improved time in the target glycaemic range • Reduced time in the hypoglycaemic range • Reduced time in the hyperglycaemic range • Patients and their families QoL metrics With improved glycaemic control, we would expect a reduction in diabetes related microvascular complications over time.

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.

7. Medtronic MiniMed 780G Insulin Pump System – Type I Diabetes

Interests

7.1. The Subcommittee reported no additional conflicts of interest with regard to this agenda item.

Application

7.2. The Subcommittee considered as supplier application from InterMed Medical Limited for the use of the Medtronic 780G system for people with type 1 diabetes mellitus who currently meet the existing pump criteria.

Recommendation

7.3. The Subcommittee recommended the MiniMed 780G system be listed with a high priority within the context of type 1 diabetes subject to the existing insulin pump criteria.

7.4. In making this recommendation, the Subcommittee noted that:

- the health needs of people with type 1 diabetes, their families/whānau and wider society
- the evidence of health benefit associated with continuous glucose monitoring, particularly when paired with insulin pump therapy
- the suitability benefits associated with an advanced hybrid-closed loop system and the increased number of people with type 1 diabetes who would experience these benefits.

Discussion

Medtronic MiniMed 780G System

7.5. The Subcommittee noted the application for funding for the Medtronic 780G MiniMed integrated pump system. The Subcommittee noted that the MiniMed 780G system is an example of an Advanced HCL system, which pairs a Bluetooth enabled insulin pump system (the MiniMed 780G™) with the Medtronic Guardian 4 CGM (Guardian Link™).

7.6. The Subcommittee noted that the pump and CGM systems interact through a proprietary algorithm (SmartGuard™ Advanced HCL technology) that automatically adjusts delivery of basal or 'background' insulin and autocorrects insulin boluses to mitigate the risk of post-prandial hyperglycaemia and keep glucose levels within a healthy range. The Subcommittee considered that these innovations were transformative for patients and their support networks, substantially reducing the level of user-engagement and burden associated with managing type 1 diabetes.

7.7. The Subcommittee noted that the MiniMed 780G system is Bluetooth enabled, sending the patients device and CGM data every 5 minutes to a cloud-based software program called Carelink via the patient's smartphone. The Subcommittee noted that this software provides detailed reports for healthcare practitioners to review and assess the patient's progress at any time from any location. The Subcommittee noted that all glucose readings are sent to the patient's smartphone via the MiniMed app allowing them to easily track their glucose values, average time-in-range, and amount of insulin delivered

7.8. The Subcommittee noted that the Guardian 4 is Medtronic's recently updated CGM system (which consists of the Guardian Sensor 4, the Guardian Connect transmitter and The Guardian Connect application). The Subcommittee noted that the system works similarly to the Guardian 3, however, does not need fingerstick calibration or diabetes treatment decisions. The Subcommittee considered that the Guardian 4 would be a suitable stand-alone CGM system along with the Dexcom G6 and could be paired with the funded MiniMed 770G in HCL system.

7.9. The Subcommittee noted that the insulin pumps can be used in Manual Mode with interaction by the patient or in Auto Mode with the pump automatically responding to CGM readings. The Subcommittee noted that both insulin bolus speeds and increments can be easily adjusted by the patient.

7.10. The Subcommittee noted the Medtronic Guardian 4 glucose sensor, transmitter and the MiniMed 780G pump are registered on the Web Assisted Notification of

Devices (WAND) database, which is a mandatory requirement for importers, exporters, and local manufacturers (Pump WAND reference: 200330-WAND-6UET8D, Glucose Sensor WAND reference: 071010-WAND-77U84E, Glucose Transmitter WAND reference: 071009-WAND-77T9ZC).

7.11. The Subcommittee noted that the MiniMed 780G insulin pump is indicated for use by individuals aged 7 - 80 years with type 1 diabetes whose total daily dose of insulin is 8 units per day or more. The Subcommittee considered, however, that patients of all ages would benefit significantly from AHCL systems, particularly in children with silent hypoglycaemia or extreme insulin sensitivity, and that it would be appropriate to use in manual mode with parental supervision in this setting.

7.12. The Subcommittee noted the following trials provided by the supplier that support the efficacy and safety of AHCL systems for improving glycaemic control in people with type 1 diabetes:

- Bergenstal et al. Lancet. 2021 Jan 16;397(10270):208-219: FLAIR, a multi-centre randomised cross-over trial comparing the MiniMed 780G (AHCL) with the MiniMed 670G (HCL) in 112 patients aged 14 – 29 years old with a clinical diagnosis of type 1 diabetes with a duration of at least 1 year at baseline. The trial deployed a run-in period using sensor augmented pump therapy and the primary outcome measures were percentage of time spent in hyperglycaemia (>180 mg/dL) during the daytime and the percentage of time spent in severe hypoglycaemia (<54 mg/dL) over 24 hours. The Subcommittee noted that the use of AHCL resulted in a significant 4%-point increase in TIR compared with HCL (67% vs 63%; P<0.001) and that patients using AHCL spent less time in hyperglycaemia (time above range) with no increase in time spent in hypoglycaemia (P<0.001).

- Collyns et al. Diabetes Care 2021 Apr; 44(4): 969-975: a New Zealand-based, randomised, open-label, two-sequence crossover study comparing the MiniMed 670G insulin pump HCL with sensor-augmented pump therapy with predictive low-glucose monitoring. The study consisted of two 4-week-long intervention periods separated by a 2-week washout period. The Subcommittee noted that HCL improved time in the target range, 3.9–10.0 mmol/L (70–180 mg/dL), compared with SAP + PLGS by 12.5 ± 8.5% (70.4 ± 8.1% vs. 57.9 ± 11.7%, respectively; P < 0.001). The Subcommittee noted that the greatest improvement in time in range was observed overnight (18.8 ± 12.9%) and in the adolescent cohort (14.4 ± 8.4%).

- The Subcommittee noted that the supplier provided a further abstract from this study demonstrating that AHCL was favoured over SAP + PLGS in a number of QoL, treatment satisfaction, & sleep quality measures. The Subcommittee considered that while the study population may not be representative of the wider pump population, the fact that it is New Zealand based research likely improved the generalisability of the findings.

- De Bock et al. Diabetes Technol Ther. 2018 20(10):693-697: an open-labelled, parallel-arm, RCT to determine the incidence of severe and moderate hypoglycaemia in adolescents aged between 13 – 27 years in a camp setting when using a HCL system when compared with standard insulin pump therapy. The Subcommittee noted that the intervention arm

started with poorer glucose metrics in terms of TIR and demonstrated a greater improvement (Change in TIR 19% v. 42%)

- Paldus et al. Diabetes Technol Ther. 2019. 21(1):56-58: a two-stage, randomised crossover study comparing standard HCL with AHCL in people with type 1 diabetes. The Subcommittee noted that relative to standard HCL, AHCL use significantly decreases closed-loop exits (3.5 [3.1] per week vs. 0 [0.0] exits per week; P = 0.004) and alerts (8.6 [5.8] per week vs. 3.9 [2.8] per week; P = 0.01), and tended to improve glycaemia without compromising safety, despite multiple food and exercise challenges during the study.

- Hood et al. Diabetes Technology & Therapeutics. 2021. Ahead of print: a randomized, open-label, two-period crossover trial to report the lived experience of using a Medtronic Advanced Hybrid Closed-Loop (AHCL) system in comparison to first generation hybrid closed-loop (HCL) system in adolescents and young adults with type 1 diabetes. The Subcommittee noted that AHCL use was associated with improved glucose monitoring satisfaction when compared with HCL and that satisfaction was greater in those participants who had more appreciable glycaemic benefit and stayed in Auto Mode more often.

7.13. The Subcommittee also noted the systematic review and network meta-analysis conducted by Pease et al. (2020), based on 52 RCTs (including 3,875 participants) comparing various diabetes management technologies (Pease et al. Diabetes Technol Therap. 2020. 22(5):411-421). The Subcommittee noted that the results of this review indicated that in terms of HbA1c reduction, both integrated CGM and CSII systems and CGM + MDI were both clinically & statistically significant, with integrated pump systems demonstrating the highest composite score. The Subcommittee noted that sensitivity analyses revealed that integrated insulin pump and CGM systems with hybrid closed loop capability appeared best for HbA1c reduction when compared to other integrated pump systems. Furthermore, the Subcommittee noted that with respect to percent time in the target range, closed loop systems were superior to all other technologies, and that CGM was superior to SMBG when used with MDI. The Subcommittee noted that in terms of reduction in hypoglycaemic events (both severe and non-severe) comparisons across diabetes management modalities were largely inconclusive, owing to the endogenous uncertainty within the included trials.

7.14. The Subcommittee also noted the following observational studies provided by the supplier:

- Nimri et al. Diabetes Technol Ther. 2021. (4):268-276.

- Tirosh et al. Diabetes. 2020. 69 (Supplement 1)

- Lee et al. 2019. 21(9):499-506.

- Biester et al. Diabetes Technol Ther. 2017. 19(3):173-182.

- Zhong et al. Diabetes Technol Ther. 2016. 18(10):657-663

7.15. The Subcommittee considered that the evidence for the efficacy of integrated pump systems, particularly AHCL systems, is limited given their recent development and the rapid product lifecycle of these technologies. However, the

Subcommittee considered that ACHL systems have the potential to significantly reduce the incidence of complications associated type 1 diabetes, including diabetic ketoacidosis.

7.16. The Subcommittee considered that there is a learning curve associated with initiation on an integrated pump system, but that when patients become familiar with the products there is very little patient involvement and that patients stay in Auto-Mode for a majority of the time. The Subcommittee considered that patients would be able to relax carbohydrate counting as a result.

7.17. The Subcommittee noted that the evidence is very much emerging and that a number of trials assessing the efficacy of AHCL systems are underway: such as the ADAPT trial, an ongoing prospective, open-label, multi-centre RCT (including up to 20 sites in EMEA region) Randomised Controlled Trial designed to investigate the effect of AHCL on A1C compared with MDI plus FGM or CGM in sub-optimally controlled adult patients with type 1 diabetes.

7.18. The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for the MiniMed 780G if it were to be funded in New Zealand for people with type 1 diabetes who meet the current insulin pump criteria. 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 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	Eligible patients with Type 1 diabetes.
Intervention	• Minimed 780G insulin pump system – 1 per 4-year period • Guardian 4 Transmitter – 1 per year • Guardian 4 sensor – 60 per year
Comparator(s) (NZ context)	SMBG + MiniMed 640G pump system SMBG + T: slim pump system
Outcome(s)	The key therapeutic intent of CGM systems is to improve the user's glycaemic control as measured by: • A reduction in hypoglycaemic events • A reduction in HbA1c • Improved time in the target glycaemic range • Reduced time in the hypoglycaemic range • Reduced time in the hyperglycaemic range • Patients and their families QoL metrics With improved glycaemic control, we would expect a reduction in diabetes related microvascular complications over time.
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.

8. Insulin Pump Review

8.1. The Subcommittee noted that Phamac began funding insulin pumps in 2012 when it entered into an agreement with New Zealand Medical and Scientific for Animas 2020 insulin pump and consumables. The Subcommittee noted that access was managed through an Insulin Pump Panel, which assessed applications against eligibility criteria. In 2016 the Insulin Pump Panel was disestablished to enable access to insulin pumps via the Pharmaceutical Schedule for four funded settings:

- Permanent neonatal diabetes
- Severe unexplained hypoglycaemia
- HbA1c
- Previous use before 1 September 2012

8.2. The Subcommittee noted that Pharmac staff received correspondence in April 2021 from the clinical leads of five DHB's raising issues with the current insulin pump special authority criteria.

8.3. The Subcommittee noted that the authors suggested changes to remove or reduce the lower limit for glycaemic control (i.e., HbA1c <53mmol/mol) for those experiencing significant hypoglycaemia.

8.4. The Subcommittee noted that the authors reported that the renewal criteria adversely impact adolescents, young adults, and those of non- European ethnicity as these groups appear to experience higher rates of discontinuation of pump therapy. The Subcommittee noted the request that these criteria be relaxed and allow greater leeway for those known to experience elevations in HbA1c (i.e. youth and non-European population groups).

8.5. The Subcommittee noted two studies as supportive evidence (Wheeler et al. 2019; 132:78-89 and Hennessey et al. 2020; 38:2245-2290), both of which utilised data from nationally held collections to investigate the uptake of insulin pumps over time. Using logistic regression analysis, the researchers were able to calculate the sociodemographic predictors of both insulin pump uptake and cessation (due to not meeting the renewal criteria).

8.5.1. Wheeler et al. NZMJ. 2019; 132:78-89 – examined uptake of publicly funded pumps from 2012 – 2016 and the sociodemographic characteristics associated with uptake. The study reported that proportion of T1D patients using continuing on subcutaneous insulin infusion (CSII) increased from 1.6%

in 2012 to 11.3% in 2016, but that the speed of uptake varied significantly by DHB, residence, ethnicity, degree of deprivation, age, and gender.

8.5.2. Hennessy et al. Diabet Med. 2020; 38:2245-2290- examined the loss of access (cessation rate), to publicly funded pumps between 2012 – 2018 and the sociodemographic characteristics associated with both access and cessation. The study reported that reduced access to CSII was associated with increasing age, male gender, Māori and Pasifika ethnicity, and lower socio-economic status. Furthermore, a total of 293 patients between 2012 and 2017 ceased using a pump in the following year, approximately 4% of patients per year. Cessation was inequitably distributed in youth (aged 10 – 29 years), those in the highest deprivation quintiles, and non-Europeans, in particular Māori (Odds ratio = 2.07 [1.37–3.03]) and Pasifika (OR = 2.98 [1.28–6.09]).

8.6. The Subcommittee considered that the current criteria should be reviewed in view of the funding applications received for glucose monitoring and integrated pump systems. In particular, the Subcommittee considered that the current glycaemic ranges be reviewed, noting that they tend to preclude patients who work extremely hard to reduce their HbA1c but are still at risk of severe hypoglycaemia, as well as patients with extremely high HbA1c who stand to benefit significantly from both CGM and insulin pump therapy.

8.7. The Subcommittee considered that while the existing renewal criteria were useful sources of extrinsic motivation, they may not be well suited to adolescent patients in the current form. The Subcommittee noted that adolescents under undergo significant physiological changes, such that maintaining glycaemic control in line with the current criteria can present a barrier to continuation.

8.8. The Subcommittee considered that Pharmac should also review the causes for increased Māori and Pacific cessation rates to ensure that the current renewal criteria appropriately meet the health needs of Māori and Pacific peoples.

8.9. The Subcommittee considered that it would be useful for Pharmac to engage with key stakeholders in this area before drafting revised Special Authority criteria for the Subcommittee to consider at the next meeting.

Insulin pump proposals

8.10. The Subcommittee noted that Pharmac had received commercial proposals to fund additional insulin pumps. The Subcommittee considered that while there was no significant unmet health, an additional pump option would provide patients and clinicians with a greater level of choice.

8.11. The Subcommittee noted that they had limited experience with either the DANA-i or YposMed insulin pumps and that the two currently listed pumps satisfied the existing health need.

8.12. The Subcommittee considered that individual assessment of any applications to fund additional pumps would be required to ensure suitable efficacy and safety due to their significant variance in functionality. The Subcommittee considered that Pharmac should consult with users and clinicians with greater experience with any additional pumps as part of such assessment.