Diabetes Subcommittee of PTAC
Meeting held 10 October 2016

(minutes for web publishing)

Diabetes Subcommittee minutes 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 minutes 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.

These Subcommittee minutes were reviewed by PTAC at its meeting 9 & 10 February 2017, the record of which will be available in due course.

Record of the Diabetes Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 10 October 2016

1 Therapeutic Group Review

Horizon scanning

1.1 The Subcommittee noted several products for people living with diabetes that had not been reviewed for funding but may be of interest in the future: smart glucose monitoring devices eg. Freestyle Libre supplied by Abbott, continuous glucose monitoring systems (CGMS) and closed loop systems involving insulin pumps and CGMS (also known as artificial pancreas).

NPPA summary

1.2 The Subcommittee noted the list of Named Patient Pharmaceutical Assessment (NPPA) applications in the diabetes and diabetes management therapeutic group from 17 March 2015 to 7 September 2016.

1.3 The Subcommittee noted that four NPPA applications for insulin detemir had been received, and that three of had not met the NPPA principles while another one had not provided further information when requested. The Subcommittee noted that insulin detemir had been considered by PHARMAC and was currently on the options for investment list. The Subcommittee noted that the NPPA process is designed for individual assessment, rather than assessment for a group of patients and that as insulin detemir had been considered through the Pharmaceutical Schedule application process, a NPPA application for this would have to demonstrate that the individual patient who the application is for is different from the group that was considered.

Insulin pumps and consumables

1.4 The Subcommittee noted that PHARMAC was planning on running a competitive process for insulin pumps and consumables and sought advice from the Subcommittee on considerations to be made before running a Request for Proposals (RFP).

1.5 The Subcommittee considered that software was commonly used by health care professionals to download patient's insulin pump data and that the ability to download data from a pump should be considered when running a competitive process for insulin pumps and consumables.

1.6 The Subcommittee considered the implementation of any change in insulin pumps would be complex and that training patients to use insulin pumps was time intensive for both healthcare professionals and patients and if a change was made to the funded pumps, implementation activities for training both groups would take a reasonable length of time and would need to be carefully considered.

1.7 The Subcommittee considered that a patient who was well managed on their current insulin pump who changes to an alternative insulin pump may notice changes in their glycaemic control. This possible change in glycaemic control would need to be taken into consideration when these patients were applying for insulin pump and consumables renewal under the current Special Authority criteria, if a change of insulin pumps was made as a result of any competitive tender process.

1.8 The Subcommittee considered that PHARMAC should be aware of a future development in the insulin pump market, in particular the bihormonal pump (a pump that administers insulin and glucagon) and developments in the "artificial pancreas" field.

1.9 The Subcommittee noted that the number of steel cannulas dispensed had continued to increase, relative to other infusion set types. The Subcommittee considered that this was likely to be due to steel cannulas being more popular, in practice, than teflon cannulas as steel cannulas seem to stay in place better. Members considered that this was an especially important factor for children and adolescents who were active and played sport.

1.10 The Subcommittee considered it would be good to review the numbers of patients (initials and renewals), versus the forecast at the next Subcommittee meeting.

2 Matters Arising – Needle use

2.1 The Subcommittee noted that at its October 2015 meeting, the Subcommittee had recommended that PHARMAC undertake a literature review to determine the available evidence regarding the number of times an insulin needle could be used by a person injecting themselves with insulin before discarding it. Members noted this was in response to correspondence received in late 2015 from a person with diabetes regarding the current maximum number of needles allowed per prescription.

2.2 The Subcommittee noted that the correspondent's primary concerns regarding the reusing of needles were the risk of infection from potentially contaminated needles after the first use, lipodystrophy, and the safe storage of unsheathed needles.

2.3 The Subcommittee reviewed information from PHARMAC's literature search and considered, in particular, the evidence from a large systematic review and meta-analysis (Zabaleta-del-Olmo et al In J Nurs Stud. 2016 Aug;60: 121-32). The Subcommittee considered there was no available robust evidence at this time to support, or refute, the single use of needles over multiple use of needles.

2.4 The Subcommittee considered that the manufacturers of needles indicated on the packaging that these were single-use only. The Subcommittee noted that its previous comments regarding the use of insulin needles up to six times was based on anecdotal, clinical experience. Members considered that many patients were likely to use a needle multiple times, and those patients who wanted to use a

needle once before discarding it were able to do so by receiving multiple prescriptions.

2.5 The Subcommittee considered that patients who preferred to use needles once only were already doing so, and if the maximum number of needles per prescription was to be increased, it was unlikely to have a significant impact on the overall number of needles used and therefore unlikely to have a significant financial impact. The Subcommittee noted the potential for financial risk from stock piling, if all patients started to receive prescriptions for 200 needles. The Subcommittee considered that there are also patients who are reluctant to change their needles regularly. Members considered that because all patients would not want to receive the maximum number of needles per prescription, the financial impact of increasing the maximum number of needles per prescription may be less than anticipated.

2.6 The Subcommittee noted that insulin pen needles are listed on the Pharmaceutical Schedule up to a maximum of 100 needles per prescription. The Subcommittee considered that an alternative to increasing the maximum number of needles per prescription, whilst minimising the risk of stock piling, would be to include a repeat on needle prescription eg. 100 needles per prescription with one repeat, which would increase the maximum number of needles available per prescription to 200 needles for patients who needed them. The Subcommittee **recommended** PHARMAC conduct analysis on the potential budget impact of increasing the maximum number of needles available per prescription by including one repeat per prescription.

3 Matters Arising – New Antidiabetic agents

3.1 The Subcommittee noted that the new antidiabetic agents dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors had undergone review by both PTAC and the Subcommittee, and that in general, the evidence reviewed to date has indicated that all agents had similar effects on reducing HbA1c by approximately 0.5% to 1%. The Subcommittee noted that all agents had been given a low priority for funding by PTAC, but the Subcommittee itself had earlier recommended medium and high priority.

3.2 Members were not aware of any information based on treatment efficacy that would have led to a lower priority over the period 2008 (when the first of these “new” agents was reviewed for funding) to 2014, and note that subsequently during 2015-2016 there had been emerging evidence of additional benefit with some of these agents.

3.3 The Subcommittee noted that an application for the combination agent dapagliflozin and extended release metformin (Xigduo XR) was reviewed by PTAC in May 2016 and that PTAC recommended that this application be declined. The Subcommittee noted PTAC’s view, that the individual agents of Xigduo XR were not currently listed on the Pharmaceutical Schedule and that the combination formulation was more expensive than the individual agents alone. The

Subcommittee noted PTAC's view, that, in general, combination agents should not be considered unless each agent in the combination formulation was registered and funded in New Zealand.

3.4 The Subcommittee noted that at its August 2014 meeting it developed a proposed Special Authority criteria for access to the new oral antidiabetic agents, to target access to the group it considered would be most likely to benefit from treatment. The Subcommittee noted that in February 2015 PHARMAC issued a Request for Information (RFI) to inform and assist PHARMAC to determine the most appropriate funding arrangement and process. The Subcommittee noted that as part of the RFI, feedback was received on the proposed Special Authority criteria, which led to the Subcommittee revising the criteria at its April 2015 meeting to include a wider group of patients than originally proposed. The Subcommittee noted that the next step in the funding process is for economic and financial analyses, incorporating the wider patient group, to be completed and the agents to be reprioritised by PHARMAC.

3.5 The Subcommittee considered correspondence from a clinician in June 2016 regarding the new oral and injectable therapies for Type 2 Diabetes. The Subcommittee considered the letter presented a well-reasoned case including clinically-significant new evidence for the new oral antidiabetic agents; dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and combination agents.

3.6 The Subcommittee noted that this evidence had been published since PTAC's review of these agents, so had not previously been considered by the Subcommittee or PTAC, and considered that this evidence reported health benefits that had not been quantified in earlier trials.

3.7 The Subcommittee noted and considered the following studies (and supplements, where available) cited in the correspondence:

- Wanner et al. (N Engl J Med. 2016;375(4):323-34)
- Marso et al. (N Engl J Med. 2016;375(4):311-22)
- White et al. (N Engl J Med. 2013;369(14):1327-35)
- Scirica et al. (N Engl J Med. 2013;369(14):1317-26)
- Beaudet et al. (J Med Econ. 2011;14(3):357-66)
- Zinman et al. (N Engl J Med. 2015;373(22):2117-28)
- Green et al. (N Engl J Med. 2015;373(3):232-42)

3.8 The Subcommittee considered that new evidence had led to changes in diabetes treatment paradigms internationally. The Subcommittee considered that this evidence was of good quality and relevance.

3.9 The Subcommittee considered that this new evidence for new antidiabetic agents reported significant health benefits in addition to improving glycaemic control, particularly, reductions in renal complications, reductions in death from cardiovascular cause, and reductions in all-cause mortality. The Subcommittee considered that these wider benefits should be taken into account in PHARMAC's cost-utility analysis of the antidiabetic agents.

3.10 The Subcommittee considered that the previous PTAC recommendations have reflected the previous absence of any longer term safety and efficacy data, however this data had now become available. The Subcommittee considered that reductions in renal complications, reduction in death from cardiovascular cause and reduction in all-cause mortality, in addition to reductions in HbA1c, were important long term clinical measures that have now had significant results reported on in trials, and therefore considered that in light of the new evidence, PTAC should review these anti-diabetic agents again.

3.11 The Subcommittee considered that there was evidence that reported that the SGLT-2 inhibitors had additional benefits other than improved glycaemic control, including a reduction in cardiovascular disease risk, reduced risk of renal dysfunction, and weight reduction. The Subcommittee considered that broadly, the benefits of the SGLT-2 inhibitor, empagliflozin, reported in the EMPA-REG OUTCOME trial were decreased death of all cause, decreased renal disease and decreased renal dysfunction (Wanner et al. N Engl J Med. 2016 Jul;375(4):323-34). The Subcommittee considered Zinman et al. (N Engl J Med. 2015 Nov 26;373(22):2117-28), a randomised controlled trial of the effect of empagliflozin on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk of cardiovascular disease. The Subcommittee noted that Zinman et al. reported that while there were no significant between-group differences in the incidence of myocardial infarction or stroke, there was however a lower rate of the primary composite cardiovascular outcome and a 38% relative risk reduction in death from cardiovascular disease in people with increased cardiovascular risk using empagliflozin.

3.12 The Subcommittee noted and reviewed the evidence presented relating to the DPP-4 inhibitors, sitagliptin (Green et al. N Engl J Med. 2015;373(3):232-42), alogliptin (White et al. N Engl J Med. 2013;369(14):1327-35) and saxagliptin (Scirica et al. (N Engl J Med. 2013;369(14):1317-26). The Subcommittee considered that these published articles reported evidence confirming their safety in high risk populations, particularly reporting that they do not lead to weight gain or hypoglycaemia.

3.13 The Subcommittee noted and reviewed the evidence regarding the GLP-1 agonist, liraglutide in the LEADER trial (Marso et al. N Engl J Med. 2016;375(4):311-22). The Subcommittee considered that the LEADER trial reported that GLP-1 agonists have a cardioprotective effect in patients with type 2 diabetes mellitus. The Subcommittee considered that the LEADER trial reported a 13% relative risk reduction for the primary composite cardiovascular endpoint and a 28% relative risk reduction for cardiovascular death in the group treated with liraglutide.

3.14 The Subcommittee noted and reviewed the evidence reporting the cost-utility of once weekly exenatide and insulin glargine in patients with type 2 diabetes

(Beaudet et al. J Med Econ. 2011;14(3):357-66). The Subcommittee noted that the correspondence cited the published article by Beaudet et al. (2011) who reported that GLP-1 agonists are effective agents for appetite suppression and weight loss, and are reported to be cost effective in comparison to bariatric surgery.

3.15 The Subcommittee considered that, based on its interpretation of the evidence listed above, in Member's own clinical experience and contextualisation of these agents in the New Zealand setting, both SGLT-2 inhibitors and GLP-1 agonists were likely to have additional clinical benefits, and considered that the DPP-4 inhibitors may have less of an additional benefit on HbA1c, but are associated with fewer side-effects (especially hypoglycaemia) than currently available agents. The Subcommittee **recommended** that, in light of the new evidence, PTAC consider the three classes of antidiabetic agents separately rather than as a group, and consider applying separate Special Authority criteria to each one of the new classes of agents.

3.16 The Subcommittee considered that it was unable to indicate how the Special Authority criteria for the new antidiabetic agents should be changed, prior to a comprehensive review of all new evidence by PTAC. The Subcommittee considered that that the new antidiabetic agents could be used in patients who had not commenced on insulin, or in combination with insulin.

3.17 The Subcommittee considered that given the available evidence for SGLT-2 inhibitors, the revised Special Authority criteria are likely to include specific recommendations related to patients' degree of renal impairment. However, members also considered that it would be important to include patients with high cardiovascular risk in the Special Authority criteria, as these patients were the cohort in the studies (Wanner et al. 2016, Zinman et al. 2015). Members considered that there was an absence of reported evidence for patients with lower cardiovascular risk, rather than the study actively reporting negative evidence for use in that patient group. Members considered that although there is less evidence for cardiovascular benefits in patients using SGLT-2 inhibitors, there is still evidence for renal protection and improved glycaemic control.

3.18 The Subcommittee considered that following PTAC's review of the new evidence for antidiabetic agents, the Subcommittee could further revise the proposed Special Authority (SA) criteria to incorporate PTAC's recommendations for these agents. Members considered that, this could be conducted via email or teleconference with the Members, rather than waiting for the next Subcommittee meeting.

4 Diabetes health economics model

4.1 The Subcommittee noted that PHARMAC, in conjunction with the BODE3 team at the University of Otago Wellington School of Medicine and Health Sciences, is building a health economics model for diabetes, and that the new antidiabetic agents for people with type 2 diabetes are due to be re-prioritised informed in part by the cost-utility analysis derived from this model. The Subcommittee noted that

PHARMAC staff sought input from the Subcommittee to review the assumptions used in developing this model.

4.2 The Subcommittee noted the proposed diabetes health economics model and the assumptions outlined by PHARMAC staff regarding the clinical course of diabetes. The Subcommittee noted that the listed disease states were based on those in the UKPDS 82 (Clarke et al., Diabetologia 2004;47) which the Subcommittee considered was the most comprehensive model available at this stage, but that models/datasets specific to New Zealand, such as the CVD Risk Assessment for people with type 2 diabetes, the unified dataset of Auckland DHB hospital and laboratory data, and data from the PREDICT study could also be included.

4.3 The Subcommittee noted the UKPDS 82 list of disease states and outcomes which would be included in the diabetes health economic model, and considered that these were largely complete but that, for thoroughness, the effect of diabetes as a chronic disease on mental health and maternal health (on both the mother and the child), and erectile dysfunction, could be included. The Subcommittee considered that the inclusion of congestive heart failure already in this model was reassuring, as it is a prevalent and an important complication of diabetes.

4.4 The Subcommittee considered that diabetes impacted on mental health, particularly cognition, and for some people with type 2 diabetes anxiety due to the possibility of hypoglycaemia was significant. Members considered that the diagnosis of diabetes (being a chronic disease) impacted on the psychological health of people with diabetes, and consideration should be given to costs such as caregiver strain and related psychosocial issues.

4.5 Members considered that the indirect costs to the health system of maternal diabetes may also be relevant. Members considered that onset of Type 2 diabetes is occurring earlier, which impacts on the proportion of people who are presenting in pregnancy with a previous history of diabetes, and consequently have higher rates of perinatal morbidity and mortality. Members also considered that due to antenatal screening for diabetes, the number of patients diagnosed with diabetes was increasing.

4.6 The Subcommittee considered that DKA has an incidence of approximately 20-30% of first presentations of type 1 diabetes in youth, with some recurrent presentations, especially in adolescents. The Subcommittee considered that it was difficult to approximate the incidence of DKA in people with Type 2 diabetes, as relevant to the diabetes health economics model.The Subcommittee noted the 'outcomes' from the UKPDS which will be used in the PHARMAC health economics model and considered that peripheral vascular disease (PVD) could be further divided by degree of severity. Members considered that it would be appropriate to incorporate standard health economics models for heart disease and amputation into the diabetes model.

4.7 The Subcommittee considered that the rate of infection in people with diabetes may be higher than in people without diabetes, but could not identify evidence to quantify the relative extent. Members further considered that delayed wound healing was likely to occur in people with diabetes, and that wound care in this

patient population may be more expensive with respect to wound dressings and district nurse time and therefore more relevant to include in the models.

4.8 The Subcommittee noted the inclusion of myocardial infarction (primary and subsequent) in the diabetes model and considered that people with diabetes are more likely to have atypical symptoms of myocardial infarction compared with those who did not have diabetes.

4.9 Members noted that three times more Māori had lower limb amputation with concurrent diabetes than non Māori. Members also noted that rates of renal failure with concurrent diabetes were more than 5 times that of non Māori, and that Māori with diabetes are 2.8 times more likely to have renal failure than non Māori with diabetes. (2013/14 New Zealand Health Survey, Ministry of Health; National Minimum Data Set (NMDS), Ministry of Health).

4.10 Members considered that the prevalence of hospitalisations in Māori with diabetes was significantly greater than non Māori, and that rates of mortality were also higher in Māori compared with non Māori.

4.11 The Subcommittee noted the inclusion of end stage renal failure in the health economics model and considered that patients with diabetes and renal failure were more likely to have poorly controlled blood pressure and were at a greater risk of cardiovascular death. The Subcommittee considered that care of these patients was primarily managed by renal specialists, and endocrinologists would manage a patient's insulin regimen.

4.12 The Subcommittee noted the inclusion of blindness and exclusion of intermediate vision states in the diabetes health economic model. The Subcommittee considered that most costs to the health system occurred before patients were clinically blind, such as regular testing for retinopathy, vascular endothelial growth factor inhibitors (VEGF, including bevacizamab, aflibercept), vitrectomy, or laser therapy. Members noted that significant specialist ophthalmology resources are used in in the treatment of diabetic retinopathy and macular disease.

4.13 With respect to PHARMAC prioritising the new antidiabetic agents, the Subcommittee considered that the health economics model should not focus on the absolute decrease in HbA1c (mmol/L), as HbA1c has been reported as reducing by a percentage. Members considered that the complexity of diabetes on a whole-life continuum should be considered.