Diabetes Subcommittee of PTAC
Meeting held 19 August 2014

(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 2008*.

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 on 6 & 7 November 2014, the record of which will be available in January 2015

Record of the Diabetes Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 19 August 2014

1 Canagliflozin

1.1 The Subcommittee considered an application from Janssen for the listing of canagliflozin in the Pharmaceutical Schedule.

1.2 The Subcommittee noted that canagliflozin was indicated for the treatment of Type 2 diabetes.

1.3 The Subcommittee noted that the supplier had proposed the following Special Authority criteria if canagliflozin was listed on the Pharmaceutical Schedule:

> Special Authority for Subsidy
>
> Initial application from any prescriber, valid for 6 months.
>
> > 1. Patient has received metformin at maximum tolerated dose for at least 6 months with inadequate glycaemic control (failure to reach agreed HbA1c target) and a sulphonylurea AND pioglitazone are contraindicated or are not tolerated
> >
> > OR
> >
> > 2. Patients have received two subsidised oral hypoglycaemic therapies at maximum tolerated doses for at least 6 months with inadequate glycaemic control (failure to reach agreed HbA1c target).
>
> Application for renewal from any practitioner, valid for 6 months so long as:
>
> > 1. Patient has received an HbA1c reduction of 5 mmol/mol from baseline: AND
> >
> > 2. Patient continues to benefit from treatment.
>
> Treatment with canagliflozin should be discontinued when eGFR is < 45 ml/min/1.73 m^2 or when initiation of insulin therapy is required due to disease progression.

1.4 The Subcommittee noted the evidence provided in the application. Members noted that there was only one comparative study with an active agent, sitagliptin. Members considered that based on the evidence provided the reduction in HbA1c appeared to be between 5 and 10 mmol/mol. Members noted that major side effect appeared to be a risk of urinary tract or genital infections.

1.5 The Subcommittee also noted that the long term safety risk of canagliflozin was unknown as it was a relatively new agent. Members noted the initial bladder cancer signal for dapagliflozin. Members considered that this signal was an early warning for monitoring at this stage and that it was possible that this could be a class effect. The Subcommittee considered that PHARMAC should monitor clinical information regarding this cancer signal moving forward.

1.6 The Subcommittee noted that this was the second application for a sodium glucose co-transporter (SGLT2) inhibitor. Members noted that the Subcommittee had recently considered dapagliflozin. Members noted that the current recommendation for dapagliflozin was funding with a low priority.

1.7 The Subcommittee noted the evidence provided suggested that the clinical outcomes from canagliflozin were consistent with those achieved with therapy from dapagliflozin.

1.8 The Subcommittee noted that canagliflozin had similar clinical effects on HbA1c as the dipeptidyl peptidase-4 inhibitors (DPP4-inhibitors) and glucose-like peptide-1 agonists (GLP-1s) and also with respect to weight change and blood pressure. The Subcommittee considered that there was no evidence of any clinical advantages over dapagliflozin. Members noted that the Subcommittee would be considering funding of all new agents later in the meeting.

1.9 The Subcommittee noted that canagliflozin would benefit those at risk of symptomatic hypoglycaemia and where metformin had not been successful or not tolerated.

1.10 The Subcommittee **recommended** funding of canagliflozin with a low priority in line with dapagliflozin.

The Decision Criteria particularly relevant to this recommendation are: The Decision Criteria particularly relevant to this recommendation are: (i) the health needs of all eligible people within New Zealand; (ii) the particular health needs of Maori and Pacific peoples; (iv) the clinical benefits and risks of pharmaceutical; (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.

2 New Agents Review

2.1 The Subcommittee noted that there were currently 3 classes of unfunded agents for the treatment of type2 diabetes, dipeptidyl peptidase-4 inhibitors (DPP4-inhibitors), glucose-like peptide-1 agonists (GLP-1s) and sodium glucose co-transporter (SGLT2) inhibitors. The Subcommittee noted its previous minutes relating to these agents.

2.2 Members noted that currently all new agents were recommended for funding with a low priority. Members **recommended** the following Special Authority Criteria, previously recommended for DDP4s and GLP-1s could apply to all new agents (including SGLT2s):

Initial application from any medical practitioner. Approvals valid for six months for applications meeting the following criteria:

1. Either:
   1.1. Patient is not achieving effective control of HbA1c despite treatment with maximum tolerated doses of metformin and sulphonylurea for at least 6 months; or
   1.2. Patient is not achieving target HbA1c despite treatment with maximum tolerated doses of sulphonylurea and metformin is contraindicated; or
   1.3. Patient is not achieving target HbA1c on maximum tolerated doses of metformin for the previous 6 months and is unable to use insulin or sulphonylureas because the risk of severe symptomatic hypoglycaemia is unacceptable in the opinion of the treating physician
2. Patient is not prescribed insulin
3. It is anticipated that a reduction in HbA1c of 5 mmol/mol would achieve the HbA1c target for that patient

Renewal from any medical practitioner. Approvals valid for two years for applications meeting the following criteria:

1. Patient has achieved an HbA1c reduction of at least 5 mmol/mol from baseline and;
2. Patient is not prescribed insulin

2.3 The Subcommittee noted that the previous recommendation relating to the new agents not being co-prescribed with insulin was based on fiscal risk and if PHARMAC could resolve the budget impact and cost effectiveness issues relating to co-prescribing then there would be no clinical reason not to allow co-prescribing.

2.4 The Subcommittee noted that all of the new classes of agents (DDP-4, GLP1s and SGLT-2s) for type 2 diabetes had signals for cancer identified.

2.5 The Subcommittee noted that the newest class of agents, SGLT2 inhibitors, lowered the plasma glucose concentration by inhibition of glucose reuptake in the kidney, without weight gain. The Subcommittee also noted that SGLT2's displayed the least in-class differences and the therapeutic advantages were weight loss, lowering HbA1c and reduction in blood pressure.

2.6 The Subcommittee noted that SGLT2's were not to be prescribed for patients with renal impairment, which was a large proportion of patients. The Subcommittee also noted that a side effect of SGLT2's was perineal mycoses which may limit suitability for some patients.

2.7 The Subcommittee noted that GLP-1's were the most "physiological" new agents and appeared to have a slightly greater reduction in HbA1c. The most common side effect was mild to moderate nausea. The Subcommittee also noted that administration was by injection only and that international data suggested that approximately 50% of patients discontinued treatment within one year.

2.8 The Subcommittee noted that GLP-1s increase the incretin effect in patients with diabetes mellitus, stimulating the release of insulin. Members noted that the GLP-1s had additional effects in reducing glucagon, slowing gastric emptying and inducing satiety. The Subcommittee considered that in clinical practice GLP-1s were likely to be associated with significant reductions in HbA1c, weight loss and had a low risk of hypoglycaemia.

2.9 The Subcommittee noted that DPP-4 inhibitors displayed the most in-class variability in metabolism. Known side effects were nausea and congestive heart failure. The Subcommittee also noted that DPP-4 inhibitors were well tolerated in short-term studies and there were no effects on body weight or risk of hypoglycaemia. Members noted that DDP-4s were the only class of new agents that could be used in patients with a glomerular filtration rate below 30, i.e. in patients with severe chronic kidney disease.

2.10 The Subcommittee noted that clinicians would prefer to have all three classes of agents funded to allow greater choice of therapeutic agent. The Subcommittee considered that depending on cost it may be appropriate for only one class of new agent to be funded out of the three classes for primary use. The Subcommittee considered that depending on the primary class of medication chosen there may be a clinical need for a second agent, particularly in patients with deteriorating renal function. The Subcommittee noted that a second agent may be required for patients intolerant to a single primary agent.

2.11 The Subcommittee considered that if cost neutral to the individual products a combination agent with metformin would be a useful agent to reduce pill burden.