Diabetes Subcommittee of PTAC meeting held 21 August 2009

(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 that contain a recommendation are 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.

Contents

1 Blood ketone test strip restriction review

1.1 The Subcommittee reviewed the endorsement restriction applying to blood ketone test strips that were listed on the Pharmaceutical Schedule from 1 July 2009 with the following restriction:

> Patient has type 1 diabetes and has had one or more episodes of ketoacidosis (excluding first presentation) and the prescription is endorsed accordingly. Maximum quantity of 2 packs per annum. No further prescriptions will be subsidised.

1.2 The Subcommittee noted the consultation responses received by PHARMAC before the approval of funding for ketone blood test strips. Members noted the concerns raised about limiting the number of subsidised test strips (especially for insulin pump users) and a suggestion that funding should be made available from initial diagnosis of type 1 diabetes and not only following presentation of ketoacidosis after diagnosis.

1.3 The Subcommittee considered that the restriction was unclear, in that the definition of ketoacidosis was unclear; however, the maximum number of packs per annum was clinically appropriate. Members noted that PHARMAC does not provide funding for insulin pump users and that these patients should approach DHBs if they consider funding for ketone testing is inadequate with pump use.

1.4 The Subcommittee considered that previous symptomatic episodes of ketosis were a more appropriate criterion versus presentation of ketoacidosis because the benefit of blood ketone testing was to prevent hospitalisations in the first place. The Subcommittee considered that patients, particularly children or the elderly, who are unable to provide urine samples for ketone testing, should also be able to access blood ketone test strips.

1.5 The Subcommittee **recommended** widening the restriction, with a medium priority, as follows (changes in bold and strikethrough):

> Patient has type 1 diabetes and has had one or more **symptomatic** episodes of ketosis ~~(excluding first presentation)~~ **or the patient is unable to provide a urine sample** and the prescription is endorsed accordingly. Maximum quantity of 2 packs per annum. No further prescriptions will be subsidised.

1.6 Members considered that if the uptake of blood ketone test strips was underestimated then the restriction proposed above could be superseded with a more relaxed restriction as follows:

> Patient has type 1 diabetes. Maximum of 2 packs per prescription [or alternatively maximum quantity of 2 packs per annum].

1.7 The Subcommittee noted that the price differential between urine and blood ketone test strips was no longer significant. The Subcommittee **recommended** that a similar maximum quantity restriction apply to urine ketone test strips if use increases significantly.

1.8 The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule; (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 Insulin pump consumables (Ace90)

2.1 The Subcommittee reviewed an application from Insulin Pumps New Zealand Ltd for the listing of its insulin pump consumables (Ace90) on the Pharmaceutical Schedule for the treatment of diabetes mellitus. The Subcommittee noted that this was the first application received for funding insulin pump consumables and that it had not been previously considered by PTAC.

2.2 The Subcommittee noted that the supplier had estimated that there were approximately 600 insulin pump users in New Zealand. The Subcommittee noted that a limited amount of funding was already provided from the Ministry of Health to 4-5 DHBs to fund patients on a regional basis. The Subcommittee noted that some DHBs also provide their own funding, however overall the funding was variable and inequitable.

2.3 The Subcommittee considered that more coordination between the various groups already involved in this field (e.g. Ministry of Health through the Quality Improvement Plan, PHARMAC and DHBs) would be beneficial as there appeared to be a duplication of work being undertaken.

2.4 The Subcommittee considered that the strength and quality of the evidence was very limited and poor. The Subcommittee considered that the greatest benefit from insulin pump use was the reduction in variability of blood glucose levels rather than a significant reduction in HbA1c. The Subcommittee noted that there was no safety information provided in the application and that there was no experience in New Zealand with this generic consumable product.

2.5 The Subcommittee noted a NICE technology appraisal of continuous subcutaneous insulin infusion for the treatment of diabetes mellitus provided by PHARMAC and a memo from the Ministry of Health on the funding of insulin pumps.

2.6 The Subcommittee considered that targeting funding of insulin pumps and consumables was critical as only a subgroup of patients would benefit from this mode of insulin delivery. Members noted that any funding would require strict entry and exit criteria.

2.7 The Subcommittee noted that there were significant patient and healthcare provider training costs associated with these devices. Members noted that most suppliers currently provided technical training for their brand of pump as a service but considered that there remains a need for a substantial amount of physician, nurse and dietitian time in initiating and maintaining patients on pumps. Members noted that the supplier had not provided any information about its support to patients and the compatibility of its consumable with other insulin pumps.

2.8 The Subcommittee considered that the supplier's budgetary impact analysis was incorrect because it had not taken into account the net-effective price of insulin glargine, the increased costs that would result from the need to test blood glucose levels more frequently and the increased wastage associated with the expected increase in rapid-acting insulin use. Members agreed that there would be a small associated decrease in overall insulin use if insulin pumps were used instead of multiple daily injections.

2.9 The Subcommittee noted the University of Canterbury's cost utility analysis (CUA) commissioned by the Ministry of Health that had been provided by PHARMAC. The Subcommittee noted that the cost effectiveness of funding continuous insulin infusion is likely to exceed $100,000 per QALY. Members noted however that the CUA had not targeted any particular population of users and it considered that the cost of diabetes management complications did not appear to be included or were underestimated.

2.10 The Subcommittee considered that there would be greater value in funding insulin pump consumables, rather than the pumps themselves, to relieve DHBs from this ongoing expenditure and ensuring that these were fully funded nationally. Members noted that a nationally consistent mechanism for funding the actual insulin pumps should be implemented (possibly by lease arrangements from suppliers to DHBs). Members considered that any part funding of insulin pumps or consumable was not appropriate.

2.11 The Subcommittee **recommended** that the application to fund insulin pump consumables (Ace90) be declined because of the limited information provided in the application. The Subcommittee considered that there would likely be benefit from running a competitive process in the future for funding insulin pumps and consumables (should PHARMAC assume responsibility for funding) and that field testing of the consumables would be necessary.

3 Insulin glulisine (Apidra)

3.1 The Subcommittee reviewed an application from Sanofi Aventis for the listing of insulin glulisine (Apidra) on the Pharmaceutical Schedule for the treatment of patients with diabetes mellitus. The Subcommittee noted that this was the first application received for funding insulin glulisine and that it had not been previously considered by PTAC.

3.2 The Subcommittee noted that insulin glulisine is a human insulin analogue with a rapid acting profile. Members noted that insulin glulisine is available in either a 10 ml vial or in a pre-filled delivery pen device (Solostar). The Subcommittee noted that the supplier had provided a range of short duration studies showing non-inferiority in HbA1c reduction when compared to other rapid-acting insulin analogues.

3.3 The Subcommittee noted that the safety profile of insulin glulisine was also similar to other rapid-acting insulin analogues. Members noted that the studies had shown the safety of insulin glulisine in pre-prandial glycaemia and ***post-prandial glycaemia.***

3.4 The Subcommittee considered that insulin glulisine has the same or similar therapeutic effect as other rapid-acting insulins currently listed on the Pharmaceutical Schedule. Members considered that the dosing requirement for insulin glulisine was comparable to currently funded insulin aspart and insulin lispro.

3.5 The Subcommittee considered that there were no problems with access to alternative treatments however noted that some patients may have a preference to use the SoloStar delivery device particularly if they were already using the insulin glargine device (Lantus SoloStar).

3.6 The Subcommittee **recommended** that insulin glulisine be listed on the Pharmaceutical Schedule only if cost-neutral or cost saving to the Pharmaceutical Budget.

3.7 The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule; (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.*

4 Various diabetes products from Pharmaco

4.1 The Subcommittee reviewed a letter from Pharmaco containing information on three products that it plans to market in New Zealand the near future. The Subcommittee noted that none of the products are yet approved by Medsafe (where applicable) and that pricing information had not been provided.

4.2 The Subcommittee noted the information provided on SQ-Pen, a re-usable needle free insulin injector device. The Subcommittee considered it was similar to a product that was available in the 1990s which caused pain and local bleeding. Members noted that for use with insulin aspart, this device required patients to use pliers to remove the screw fitting from Novo Nordisk cartridges.

4.3 The Subcommittee noted the information provided on Diabetone, a multivitamin supplement specially formulated for people with diabetes. The Subcommittee noted that this was a very old product and considered that some of the ingredients may cause problems for some patients with diabetes. Members considered that there was no clinical need for such a product since other vitamin supplements were readily available.

4.4 The Subcommittee noted the information provided on Sweete, a natural sweetener that may be used as a sugar substitute for patients with diabetes. The Subcommittee considered that there was no unmet clinical need for such a product.

5 Vildagliptin (Galvus)

5.1 The Subcommittee reviewed an application from Novartis New Zealand Limited for the listing of vildagliptin (Galvus) on the Pharmaceutical Schedule. The Subcommittee noted that vildagliptin was a dipeptidyl peptidase (DPP-4) inhibitor used in the treatment of patients with type 2 diabetes. The Subcommittee noted that this was the first application received for funding vildagliptin and that it had not been previously considered by PTAC.

5.2 The Subcommittee noted that vildagliptin was indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus as monotherapy and in dual combination with metformin, a sulfonylurea, a thizaolidinedione, or insulin when diet, exercise, and a single antidiabetic agent do not result in adequate glycaemic control. The Subcommittee noted that vildagliptin is supplied as 50 mg tablets and has a recommended dose of either 50 mg or 100 mg daily. The Subcommittee noted that the supplier had proposed open access to vildagliptin within this indication.

5.3 The Subcommittee considered that the strength and quality of the evidence was moderate. The Subcommittee noted that there were 14 phase III trials provided by the supplier relevant to vildagliptin's efficacy and safety. Members noted that the trials reported the experience of almost 10,000 patients receiving vildagliptin in combination with various products compared with control groups with the primary endpoint being change in HbA1c. Members noted that toxicity endpoints were reported, but there were no data on survival, complications of diabetes and later toxicities.

5.4 The Subcommittee noted that the 14 trials fell largely into 4 design categories. The Subcommittee noted that 7 trials considered the benefit of vildagliptin in monotherapy trials (3 as monotherapy in placebo-controlled and 4 as monotherapy in active-controlled versus metformin, glitazones or acarbose). Members noted that the further 7 key trials considered the benefit in combination with other treatment regimens for patients with type 2 diabetes (4 in placebo controlled and 3 in active controlled).

5.5 The Subcommittee noted that the studies demonstrated that vildagliptin treatment was associated with greater reductions in HbA1c over time. The Subcommittee noted that in analyses of non-inferiority, the smallest clinically relevant difference was stated as 0.4%. Members considered that overall the decrease in HbA1c was small and appeared similar to other available oral therapies.

5.6 The Subcommittee noted that the supplier had omitted to tabulate data from Scherbaum (Diabetes Med 2007; 24(9): 955-61) which compared the 50 mg once daily dose with placebo in n=306. The Subcommittee noted that the results of this study found a difference of -0.3% at 1 year and -0.5% at 2 years (i.e. a smaller effect than the other studies and close to the non-inferiority margin). The Subcommittee noted that the supplier had also omitted to tabulate data from a large study by Ferrannini (Diabetes Obes Metab 2009; 11(2): 157-66). The Subcommittee noted that this study compared vildagliptin in combination with metformin with glimeprimide and metformin. The Subcommittee noted that a per-protocol analysis (n=2,190) demonstrated non-inferiority, with a difference in change in HbA1c at week 52 of +0.09%.

5.7 The Subcommittee noted that the usual duration of treatment in the supplier-included studies was 24 weeks. Members noted that the minimum duration of the studies was 12 weeks and the longest reported follow-up was 104 weeks, around 15% of subjects. Consequently, the Subcommittee considered that long-term data was insufficient.

5.8 The Subcommittee noted a systematic review and meta-analysis on the efficacy and safety of incretin therapy in type 2 diabetes that was provided by PHARMAC (Amori et al; JAMA. 2007;298(2):194-206). The Subcommittee noted that this was a useful comparator that included four studies (Ristic 2005, Pratley 2006, Mimori 2006, and Ahren 2004) that the supplier had not provided, presumably because some or all of the arms used lower vildagliptin doses (25 mg once daily – 50 mg once daily) than was proposed

for funding. The Subcommittee considered that the Amori review conflicted several of the supplier's application statements and assessments.

5.9 The Subcommittee noted that Amori et al concluded that vildagliptin increased the risk of infections, in particular in the urinary tract (relative risk ratio of 2.72), and headache (relative risk ratio 1.47). The Subcommittee note that these risks became apparent only on meta-analysis and currently the majority of patients reported have only been exposed to vildagliptin about 1 year.

5.10 The Subcommittee considered that there was a slight trend towards better efficacy in the vildagliptin treatment study arms, with the exception of vildagliptin and acarbose. The Subcommittee noted because of the mechanism of DPP-4 inhibitors that there is less risk of patients having a hypoglycaemic event compared with other therapies. The Subcommittee noted that pooled data suggests vildagliptin is not associated with weight gain, has neutral to favourable effects on lowering lipids and blood pressure and vildagliptin would seem a beneficial option where patients are intolerant to, or following failure of, other oral products. However, Members considered that overall, data from the studies demonstrated that vildagliptin provided no additional benefit in terms of control of diabetes compared to other treatment options other than placebo.

5.11 The Subcommittee considered that patients intolerant to currently funded oral products, or, those who were at increased risk of hypoglycaemia with these products would benefit most from funding vildagliptin.

5.12 The Subcommittee considered that vildagliptin has the same or similar therapeutic effect to sitagliptin (when dosed 50 mg twice daily), pioglitazone (when dosed 45 once daily), glibenclamide (when dosed 15 mg daily), glipizide (when dosed 10 mg twice daily) or gliclazide (when dosed 160 mg twice daily). The Subcommittee noted that, with the exception of sitagliptin, all of these pharmaceuticals are currently listed on the Pharmaceutical Schedule. The Subcommittee considered that vildagliptin, if listed, would be used in combination with any of the currently listed oral diabetes management products and insulin and would most likely replace ***sulphonylureas*** due to its similarity of insulin-releasing effect.

5.13 The Subcommittee considered that the suppliers predicted dosing proportion estimate (i.e. that 30% of patients would receive vildagliptin 50 mg once daily and 70% vildagliptin 50 mg twice daily) was incorrect. Members considered that vildagliptin would be prescribed at the 50 mg twice daily dose more frequently.

5.14 The Subcommittee noted that it was unsure yet of the exact place in therapy for DPP-4 inhibitors. Members considered that due to the fiscal and clinical risks of vildagliptin (namely that there was insufficient long term toxicity and clinical outcome data) that, if listed, vildagliptin should be restricted by Special Authority as a last line oral treatment for patients who had failed and/or were intolerant of established agents.

5.15 However, the Subcommittee noted that there was some evidence that DDP-4 inhibitors should be used earlier in the treatment paradigm because of the impact that they have on alpha and beta cells and that patients with a higher HbA1c received the greatest benefit. Members considered that direct agonists would more likely provide greater benefits with less potential risk than DPP-4 inhibitors.

5.16 The Subcommittee **recommended** that vildagliptin be listed on the Pharmaceutical Schedule with a low priority.

5.17 The Subcommittee noted that the supplier also had a combination vildagliptin and metformin product. The Subcommittee consider that there would likely be benefit from a combination product although it would need to be cost-neutral or cost-saving compared with funding of vildagliptin and metformin individually.

5.18 The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

6 Sitagliptin (Januvia) and sitagliptin and metformin (Janumet)

6.1 The Subcommittee considered a re-application from Merck Sharpe and Dohme for the listing of sitagliptin (Januvia) and an application for its combination sitagliptin and metformin formulation on the Pharmaceutical Schedule for the treatment of patients with type 2 diabetes.

6.2 The Subcommittee noted that it had considered an application from Merck Sharpe and Dohme for the listing of sitagliptin at its June 2008 meeting and had recommended that the application be declined. The Subcommittee noted that the re-submission included longer term data (minimum of two years) for the efficacy and safety of sitagliptin and data relating to the use of sitagliptin when co-administered with a sulphonylurea and when co-administered with a sulphonylurea and metformin. Members noted that the re-application also included safety and efficacy data for a combination product of sitagliptin and metformin.

6.3 The Subcommittee noted that the supplier proposed very broad Special Authority criteria that included sitagliptin monotherapy where metformin, sulphonylurea and pioglitazone are contraindicated, or not tolerated, and in combination with metformin and / or sulphonylurea, or pioglitazone, when diet and exercise, and/or these agents do not provide adequate glycaemic control. Members noted that the supplier proposed similar criteria for the sitagliptin/metformin combination product.

6.4 The Subcommittee noted safety and tolerability data of sitagliptin (and sitagliptin metformin combination) in patients with type 2 diabetes treated for up to two years provided by the supplier (William-Herman et al Curr Med Res Opin 2009; 25(3):569-583). The Subcommittee also noted a meta analysis by William-Herman et al (BMC Endocrine Disorders 2008; 8:14) that assessed the safety and tolerability of sitagliptin by pooling 12 large, double-blind, Phase IIb and III studies up to 2 years in duration. In addition, the Subcommittee considered several shorter duration studies that assessed the safety and efficacy of sitagliptin when co-administered with a sulphonylurea, with or without metformin.

6.5 The Subcommittee considered that the strength of evidence was good and the quality of the evidence provided was moderate. The Subcommittee noted that sitagliptin treatment

was associated with a reduction in HbA1c of around 1% in most of the studies examined and was associated with less nausea than metformin. The Subcommittee noted that sitagliptin, like other DPP-4 inhibitors, was associated with an increased risk of infection.

6.6 The Subcommittee noted that the drop out rates in some studies were very high (in some cases around 80% at 2 years). Consequently, the Subcommittee considered that long-term data was insufficient and considered that review of post-marketing data would be valuable.

6.7 The Subcommittee considered that the sitagliptin and metformin combination product would help improve compliance for some patients; however, members considered that it would mainly be a convenience factor for patients rather than addressing any particular unmet clinical need.

6.8 The Subcommittee considered that for a small group of patients sitagliptin may be beneficial if it resulted in a delay for them initiating insulin treatment (e.g. patients with a needle phobia or patients who had were restricted in their ability to continue their employment if on insulin).

6.9 The Subcommittee noted that it had considered an application for vildagliptin, an alternative DPP-4 inhibitor, and considered that there were no advantages for either chemical entity over the other. Members considered that direct agonists would more likely provide greater benefits with less potential risk than DPP-4 inhibitors as they had more specific target activity.

6.10 The Subcommittee noted that there was some evidence that DDP-4 inhibitors should be used earlier in the treatment paradigm because of the impact that they have on alpha and beta cells and that patients with a higher HbA1c received the greatest benefit. Members considered that overall the place of sitagliptin in the treatment paradigm was unclear and that overall there was no significant advantage over the use of insulin and would only delay the insulin uptake in some patients.

6.11 Subcommittee **recommended** that sitagliptin be listed on the Pharmaceutical Schedule with a low priority and **recommended** that the combination sitagliptin and metformin product be listed on the Pharmaceutical Schedule only if cost-neutral or cost saving compared with sitagliptin and metformin alone.

6.12 The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule*