Stakeholder Forum Summary
Stage 3: Type 2 Diabetes Medicines

Post-Market Review of Products used in the Management of Diabetes
Department of Health, 12 September 2013

This document is intended to provide a broad summary of the views expressed by stakeholders and only information provided at the Forum has been included. No attempt was made to reach consensus and the views and opinions should not be considered as medical advice. This Summary, along with all other comments contributed by attendees, will be provided to the Diabetes Review Reference Group for consideration.

PURPOSE AND CONTEXT

This Stakeholder Forum provided an opportunity for a broad spectrum of stakeholders to inform Stage 3 of the Post-Market Review of Products used in the Management of Diabetes, which focuses on medicines used in type 2 diabetes. The aim of the Forum was to discuss:

- appropriate treatment pathways for type 2 diabetes, particularly the role of newer medicines;
- long-term clinical benefit and safety profiles associated with type 2 diabetes medicines; and
- the appropriateness and ease of use of the current guidelines and Pharmaceutical Benefits Scheme (PBS) restrictions.

A summary of the Drug Utilisation Sub-Committee (DUSC) findings on the utilisation of type 2 diabetes medicines was presented at the Forum. Prior to the meeting, attendees were provided with a background discussion paper that included information on the Review Terms of Reference, PBS restrictions, treatment algorithms from new international guidelines, a summary of the DUSC findings, and the focus questions for the Forum.

Six focus questions were posed at the Forum to prompt discussion:

1. *What are the advantages and disadvantages of gliptins, and other potential second-line medicines, and how important are these to patients? Noting that, a recent report by the Canadian Agency for Drugs and Technologies in Health showed that there was no significant difference in blood glucose lowering between sulfonylureas and other second-line medicines, e.g. gliptins. Sulfonylureas were shown to be the best value for money, and in Australia, sulfonylureas are significantly cheaper than other second-line medicines (around $8–15 a pack versus $90–97 a pack for gliptins).*
2. *What evidence is there about the long-term clinical benefit and safety profile of gliptins and other new type 2 diabetes medicines, compared to sulfonylureas? Do patients or clinicians have any comments about the safety and long-term benefits of the newer type 2 diabetes medicines?*
3. *What are the preferred medicines in third-line therapy and why?*
4. *Are people using the Australian type 2 diabetes management guidelines? Do they need updating and why?*
5. *Continuing on from the discussion about treatment pathways, how can we ensure that newer type 2 diabetes medicines continue to provide value for money?*
6. *What are the sources of confusion and/or misunderstanding for prescribers in the PBS restrictions for type 2 diabetes medicines that may influence compliance?*

There was also an opportunity for open discussion not related to the focus questions.

Stakeholders were informed that a Stage 3 Review Report is expected to be considered by the Pharmaceutical Benefits Advisory Committee (PBAC) in 2014, before being provided to Government.

SUMMARY OF KEY DISCUSSION POINTS RAISED BY STAKEHOLDERS

- There should be a patient centred, individualised approach to treatment. Choice of therapy should be based on the patient, including consideration of age, stage of disease at consultation, preferences, likelihood of compliance, health literacy, the availability of education and support, weight, comorbidities, pregnancy, ethnicity, profession, lifestyle and activities. This needs to be considered in the context of the current evidence, and the side effect profiles and mode of action of the medicines.
- Most third-line agents are comparable to sulfonylureas in terms of HbA_{1c} lowering. However, diabetes outcomes should not be measured by HbA_{1c} levels alone. Other important outcomes include avoidance of hypoglycaemia, weight, side effects, hospitalisations, long term health outcomes and development of micro- and macrovascular complications.
- It is important to try to minimise hypoglycaemic events due to their multi-dimensional effect on patients, including quality of life, productivity, psychosocial impacts, risk of falls in the elderly, and for severe hypoglycaemia, limiting expensive hospital admissions.
- Patients should be involved in treatment choice and provided with the necessary information by their clinician to assist in this decision.
- Some patients may prefer a treatment strategy that involves earlier intervention and lower HbA_{1c} targets.
- Current treatment guidelines create confusion because they reflect the PBS reimbursement criteria and not the most current clinical evidence. The treatment guidelines should be updated to incorporate new evidence and be consolidated into a single set of guidelines. This will require collaboration between peak bodies and the National Health and Medical Research Council (NHMRC). The treatment algorithm should be evidence-based, patient centred, easy to implement in clinical practice, and should make clear the PBS requirements and criteria for subsidy. The Australian Diabetes Society and the Royal Australian College of General Practitioners (RACGP) are developing updated treatment algorithms.
- Treatment pathways need to consider prevention, education and lifestyle factors in addition to medication.

SUMMARY OF STAKEHOLDER RESPONSES TO FOCUS QUESTIONS

Q1: What are the advantages and disadvantages of gliptins, and other potential second-line medicines, and how important are these to patients?

- Dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins) are a good alternative to metformin or sulfonylureas in second-line therapy, offering better tolerability and comparable efficacy. There is a shortfall in clinical experience associated with these agents, but safety data on newer medicines are of a much higher quality and long term outcomes data are now available. However, gliptins may be associated with negative cardiovascular outcomes.
- Hypoglycaemic events are often under-recognised in type 2 diabetes patients. Symptomatic hypoglycaemic events have a multidimensional effect on the patient and have important impacts in terms of quality of life and hospitalisations.

- Gliptins are associated with fewer adverse events and also benefits in terms of weight and hypoglycaemia. These benefits improve quality of life and compliance, which in turn may lead to better long term patient outcomes.
- Gliptins are also effective when used early in the disease, but the current guidelines and PBS restrictions prevent early use. This means that doctors are compelled to prescribe these newer medicines later in the treatment cycle when some of their potential benefit may be lost.

Q2: What evidence is there about the long-term clinical benefit and safety profile of gliptins and other new type 2 diabetes medicines, compared to sulfonylureas? Do patients or clinicians have any comments about the safety and long-term benefits of the newer type 2 diabetes medicines?

- Gliptins and other third-line therapies, including sodium-glucose transport protein 2 (SGLT2) inhibitors, are comparable to sulfonylureas in terms HbA_{1c} lowering. However, glucagon-like peptide-1 (GLP-1) agonists may be slightly more effective.
- Gliptins may have benefits over sulfonylureas in lowering the rate of hypoglycaemic events and not causing weight gain. However, the most commonly used sulfonylurea in Australia, gliclazide, is often not included in clinical trials as a comparator. Gliclazide may cause less weight gain than other sulfonylureas.
- It is incongruous and a negative experience for the patient, for health professionals to prescribe medicines that may cause weight gain while recommending that their patients lose weight.
- Based on the EXAMINE trial of alogliptin, gliptins do not show adverse effects on cardiovascular health, nor do they show benefit. The SAVOR-TIMI trial of saxagliptin showed similar results, but with an increased relative risk of hospitalisation for heart failure in the treatment arm compared to placebo. There are no other equivalent findings on heart failure risks for gliptins from other trials. The EXAMINE and SAVOR-TIMI trials did not show any signals for alogliptin and saxagliptin with regard to pancreatitis or pancreatic cancer.
- Glitazones (e.g. rosiglitazone and pioglitazone) have links with heart failure.
- Research on patient reported outcomes showed higher treatment satisfaction and increased benefits for weight related quality of life effects with the use of GLP-1 agonists.

Q3: What are the preferred medicines in third-line therapy and why?

- Choice of third-line therapy should be based on the patient, including consideration of age, preferences, likelihood of compliance, health literacy, the availability of education and support, weight, pregnancy, ethnicity, profession, lifestyle and activities, and stage of diabetes, in the context of the side effect profiles and mode of action of the medicines. Microvascular and macrovascular risks, blood pressure and lipid levels also need to be considered.
- Patients should be involved in treatment choice and provided with information on the effectiveness, convenience and side effects of medicines they may be prescribed.

The following factors should be considered:

- Weight: For those who are overweight, GLP-1 agonists and SGLT2 inhibitors cause weight loss and gliptins are weight neutral. For lean patients, insulin and glitazones may be the best choices.
- Stage: For those with no beta cell function, insulin, gliptins, glitazones, GLP-1 agonists and SGLT2 inhibitors may be best; while for those with remaining beta cell function, gliptins, GLP-1 agonists and glitazones are good choices.
- Pregnancy: During pregnancy, and for women of child-bearing age, a different third-line therapy may be selected, which may include insulin. It is best to exclude glitazones.
- Profession: There may be impacts on drivers' and pilots' licenses with the use of insulin.
- Education and support: Education and support is important for patient acceptance and improved compliance. A coordinated general practitioner (GP) education program is necessary to support GPs to inform their patients and provide an appropriate level of choice.
- Hypoglycaemia: Gliptins used in combination with metformin and a sulfonylurea lead to an increase in hypoglycaemic events.

Q4: Are people using the Australian type 2 diabetes management guidelines? Do they need updating and why?

- Guidelines are being used, but their interpretation and usefulness is variable.
- The plethora of diabetes guidelines that exist is likely to be causing confusion.
- The existing guidelines should be reviewed and updated to incorporate evidence on newer medicines. Where the evidence base supports safety and effectiveness, patients should have access to all medicines. However, the guidelines should clearly state use that is, or is not, PBS subsidised, based on cost-effectiveness.
- It would be useful to have a consolidated, core set of guidelines. This will require interaction between peak bodies and the NHMRC to ensure comparability in treatment algorithms. This may be difficult to achieve if there are disagreements between organisations, e.g. on HbA_{1c} target levels.
- If a new treatment algorithm is written, then this will need to be implementable in clinical practice and translated for ease of use by GPs when considering individual patients.
- Both the Australian Diabetes Society and the RACGP are currently developing updated treatment algorithms.

Q5: Continuing on from the discussion about treatment pathways, how can we ensure that newer type 2 diabetes medicines continue to provide value for money?

- Value for money should consider real world effectiveness, be patient centred and focused on patient relevant outcomes, rather than being based solely on the results of randomised controlled trials.
- Controlling HbA_{1c} levels is very important for reducing complications, but other considerations include side effects, hypoglycaemic events, weight gain, long term health outcomes, hospitalisations and quality of life factors, such as flexibility and productivity. Where data for this is available, it should be incorporated into decision making.

- Patient quality of life factors are important to motivate patients to take their medicines, ultimately leading to better health outcomes.
- Sulfonylureas are cheaper, but newer medicines may have better quality trials and safety outcome data.
- The biggest expense in diabetes management is associated with diabetes complications and not the cost of medicines. Clinicians should take holistic approach to diabetes management that considers both short and long term outcomes.
- Other issues to consider in treatment pathways are new technologies and patient demand for individualised therapy.

Q6: What are the sources of confusion and/or misunderstanding for prescribers in the PBS restrictions for type 2 diabetes medicines that may influence compliance?

- The PBS restrictions are lengthy and there could be some confusion regarding the definitions of contraindication and intolerance to sulfonylureas. However, the lack of prescribing compliance cannot just be explained through confusion with the restrictions.
- Some clinicians may apply a broader definition of contraindication than described in the Product Information for sulfonylureas, which takes individual patient circumstances into account.
- Patient concerns and characteristics need to be accounted for when prescribing medications.
- Although the intolerance list is long, the absolute contraindication list for sulfonylureas is short. To be determined as intolerant, a patient has to try the medicine. Some prescribers are not following the PBS restrictions.
- The plethora of guidelines also contributes to confusion.
- The option of using insulin in combination with GLP-1 agonists or gliptins would be useful in obese patients with comorbidities and heart failure. This is a small, but difficult to treat group of patients. Gliptins and exenatide have TGA approval to be used with insulin[i].

ADDITIONAL PERSPECTIVES RAISED BY STAKEHOLDERS

Clinicians, Health Professionals, and Health Professional Peak Bodies

- In prescribing medicines, clinicians need to consider the clinical evidence, as well as the way that a patient lives their life and their priorities in terms of health outcomes.
- There is poor health literacy in the community, which affects patients' understanding of self-management of diabetes.
- The current guidelines provide little assistance about how to appropriately balance potential safety concerns and patient choice.
- The guidelines are currently too focussed on HbA_{1c} levels. Blood pressure, lipid levels and micro- and macrovascular risks also need to be incorporated into the treatment algorithm in a single guideline.
- GP education on translating the new guidelines into individualised therapy will be needed.
- Newer type 2 diabetes medicines may offer a more favourable therapy for some people based on efficacy and better side effect profiles.
- For some people, gliptins should be used earlier in the treatment of diabetes.

- On a conceptual level, are there enough agents available to treat diabetes and the existing medicines just need to be used more effectively? A framework is required to show what is being done well now and what could be improved upon.

Consumers and Consumer Peak Bodies

- Treatment pathways need to consider prevention, education and lifestyle factors in addition to medication. Community and school based education programs for children and parents are important to motivate people to address lifestyle factors, so that improvements in treatment outcomes and diabetes prevalence will be seen.
- Health care professionals are responsible for providing information on medicines and choice to their patients.
- The DUSC analysis highlighted the increasing PBS expenditure on type 2 diabetes medicines; however, it is important to adjust this to account for the increasing prevalence of the disease.
- The current PBS restrictions influence medicines use. If all diabetes medicines were unrestricted:
    - gliptins would take over as a second-line therapy from sulfonylureas and be used at lower HbA_{1c} levels;
    - GLP-1 agonists would be introduced earlier;
    - there would be more use of GLP-1 agonists in combination with insulin in obese patients; and
    - use of SGLT2 inhibitors would increase quickly due to their negative weight effects.
- The United Kingdom Prospective Diabetes Study (UKPDS) indicated that it may be better to engage in aggressive therapy at early disease stages, except in the elderly where there may be cardiovascular risks associated with aggressive pharmaceutical therapy.
- Anecdotally, some patients who are told by their clinician that they have 'mild type 2 diabetes', have later developed complications, and consider that they were undertreated and would have preferred a more aggressive treatment strategy.
- With type 2 diabetes, there are currently no randomised controlled studies for children 15 years and under. An increasing number of people diagnosed with type 2 diabetes are under 18 years of age and require appropriate treatments to be available.

Industry and Industry Peak Bodies

- Diabetes outcomes are not just reflected by HbA_{1c} levels. Other key elements include hypoglycaemia, weight gain, quality of life and flexibility.
- Research indicates that patients want choice and clinicians should be able to offer treatment options to patients.
- Patients want a conceptual approach to the management of diabetes that delivers a higher standard of care at the beginning of their disease. If diabetes is diagnosed early and treated appropriately, progression to the later stages of the disease may be prevented.

  Current guidelines reflect the PBS reimbursement criteria. A lack of subsidy does not necessarily mean that a medicine is clinically irrelevant.

[i] As of 1 November 2013, vildagliptin was not indicated for use with insulin on the Australian Register of Therapeutic Goods.