Submission to the PBAC Post Market Review of Products Used in the Management of Diabetes: Drug Utilisation and Listing Review

Boehringer Ingelheim welcomes the opportunity to comment on the Post-Market Review of Products Used in the Management of Diabetes (referred to as the Diabetes Review). This submission addresses the Terms of Reference related to Phase 3 of the Review, which addresses utilisation and patterns of treatment for PBS listed diabetes drugs.

Patients need access to a range of diabetes medicines

Current treatment pathway for type 2 diabetes

Type 2 diabetes is a chronic disease which can result in disability and early death. Initial management with non-pharmacological interventions such as lifestyle modification are indicated for all patients. Disease progression occurs in most patients, who require anti-hyperglycaemic agents in order to reduce diabetes complications such as chronic kidney disease, blindness and limb amputations. It is important that patients continue to have access to currently available medications as well as newer classes of diabetes drugs in order to ensure they are able to achieve optimal treatment outcomes.

The treatment algorithm most commonly used in Australia is from the Diabetes Australia and the Royal Australian College of General Practitioners (RACGP) Clinical Guidelines. It is recommended that patients first modify their lifestyle, which includes changing diet, weight control and increased physical activity. Pharmacological agents should be used if this does not result in sufficient glycaemic control over a period of six weeks. First line pharmacological therapy should be metformin, in addition to lifestyle modification. If glycaemic control is not achieved with metformin, a sulfonylurea should be used, either as monotherapy or as combination therapy with metformin.

If glycaemic control is not achieved with metformin and/or sulfonylurea, other medications need to be considered as third line therapy. Current Pharmaceutical Benefits Scheme (PBS) listed third line medications include acarbose, dipeptidyl peptidase-4 (DPP-4) inhibitors, glitazones, glucagon-like peptide-1 (GLP-1) agonists and insulin. The guidelines do not offer specific guidance as to which of these classes should be prescribed or give a preference for the use of different combination therapies. The decision to use one class of drug over another should be made on an individual patient basis, taking into consideration the specific risk and benefit profile for each class. It is important that patients have access to multiple

third line medicines as different drug classes have varying adverse effects, contraindications and precautions. There are also differences between the therapies in terms of their reimbursed indications, with different drugs able to be used as monotherapy, dual therapy and/or triple therapy. It is essential that patients have access to a broad range of treatment options so that an individualised treatment plan can be established in order to improve glycaemic control and reduce diabetes complications.

Clinical need for alternative treatment options

Recent experience with the glitazones demonstrates the importance of having multiple drug classes available to patients. The glitazones are associated with a number of safety concerns and their use has been restricted by some regulatory authorities. Rosiglitazone was initially PBS listed for dual and triple therapy in 2003, however post-marketing studies identified a significantly increased risk of myocardial infarction. Consequently, the Therapeutic Goods Association (TGA) removed triple therapy and dual therapy with insulin from the approved indication. The PBS listing for these indications was removed in late 2008. In September 2010, the European Medicines Agency (EMA) removed marketing authorisation for Avandia® (rosiglitazone) and the combination products Avandamet® (rosiglitazone plus metformin) and Avaglim® (rosiglitazone and glimepiride) (EMA, 2010). The Food and Drug Administration (FDA) implemented a restricted access program, with patients only allowed access to rosiglitazone if they were unable to achieve glycaemic control on any other medication and only if the risk profile has been shared with the patient (FDA 2010). The TGA required a boxed warning to be included in the product information (PI) stating that '*Avandia® has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short-term clinical studies compared to combined active/placebo control (2.00% versus 1.53%, respectively), particularly in those who needed several antidiabetic drugs or nitrates'*.

The cardiac risk profile is similar for pioglitazone. After a review of postmarketing adverse event reports, the FDA determined that an updated label with a boxed warning on the risks of heart failure was needed for the entire thiazolidinedione class (FDA 2007). The PI for pioglitazone states that it can cause or exacerbate congestive heart failure. Furthermore, pioglitazone has recently been associated with an increased risk of bladder cancer. In June 2010, the FDA issued a safety announcement warning of an increased risk of bladder cancer in patients who receive pioglitazone. The results showed that there was no significant increase in the risk of bladder cancer in patients exposed to pioglitazone compared to patients never exposed to pioglitazone (FDA 2011). However, the risk of bladder cancer increased with increasing dose and duration of pioglitazone use. The FDA also discussed a

retrospective cohort study using data from the French National Health Insurance Plan. There was a statistically significant increase in the risk for bladder cancer in patients exposed to pioglitazone compared to patients exposed to other anti-diabetic agents. Based on this data, France has suspended the use of pioglitazone and Germany has recommended that new patients do not initiate pioglitazone. The TGA has issued a safety alert following a review of the data (TGA 2011). A recent retrospective cohort study also reported a significantly increased risk of bladder cancer in patients who received pioglitazone (Azoulay *et al* 2012).

Pioglitazone is used in Australia despite these safety concerns. It has also been recently reported that Australians have joined a class action suit against the manufactures of pioglitazone (SMH, 2013). Pioglitazone has the broadest indication of the reimbursed diabetes drugs and is the only oral agent which can be used as triple therapy and in combination with insulin. This restricts the treatment options available to prescribers. DPP-4 inhibitors and a GLP-1 agonists are PBS listed and provide safer alternative treatment options, although with fewer reimbursed indications. Newer drugs such as sodium glucose co-transporter-2 (SGLT-2) inhibitors are registered in Australia, but are currently not reimbursed. Therefore, there are currently limited treatment choices for clinicians, particularly when patients would be most appropriately treated with triple therapy or in combination with insulin but are unable to receive pioglitazone due to contraindications or safety concerns. There is a clinical need for alternative treatment options for patients who would be more appropriately treated with other anti-diabetic agents.

Difficulty achieving a new PBS listing or indication for diabetes medicines

It is important that patients have access to the full range of clinically appropriate drugs so that clinicians can individualise treatment options for each patient. However, it has become increasingly difficult to achieve a PBS listing for new diabetes medicines and expand existing indications, especially as the prices of comparator drugs in the F2 formulary are reduced. While it remains essential that the PBAC recommend clinically effective and cost effective medicines, it is important that the framework for assessment is flexible enough to incorporate the clinical evidence available.

Barriers to new PBS listings for triple therapy despite treatment need

Patients who tolerate metformin and a sulfonylurea but require additional glycaemic control with triple therapy are able to access pioglitazone and exenatide triple therapy through the PBS. Pioglitazone is administered orally while exenatide is administered as an injection. The safety concerns associated with pioglitazone have been discussed in detail above, and pioglitazone may not be an appropriate option for many patients. Patients and clinicians are

understandably reluctant to progress straight to injectable agents if this is not required. However, patients who are contraindicated to pioglitazone or who are concerned about the safety profile have no other triple therapy option but exenatide. Patients who are unable or unwilling to use an injectable agent are able to use a DPP-4 inhibitor, but must cease either metformin or a sulfonylurea to meet the current PBS eligibility criteria. This is not a preferred treatment option as the patient must initiate a new medication at the same time as removing an existing one. This strategy may not provide optimal glycaemic control. This also complicates clinical decision making as a loss of glycaemic control could either be a poor response to the DPP-4 inhibitor or a result of ceasing metformin or a sulfonylurea.

Linagliptin is TGA registered for use as triple therapy and sought a PBS listing for this indication in July 2012. The most commonly prescribed triple therapy option is pioglitazone and this is therefore the comparator for any new diabetes medication requesting reimbursement for triple therapy. There are no head-to-head trials of any gliptin triple therapy and pioglitazone triple therapy due to the increasing safety concerns associated with pioglitazone. The difficulty of demonstrating non-inferiority to pioglitazone triple therapy without head-to-head data was highlighted by the PBAC as part of the evaluation of the July 2012 submission. There was a marked degree of heterogeneity in the pioglitazone trials, which limited the ability of the indirect analysis to demonstrate non-inferiority. The PBAC noted that *"the differences in the study design of the linagliptin and pioglitazone trials (e.g. trial duration, dosage regimens, co-administered therapies and patient populations/trial locations) add additional uncertainty to the indirect comparison of HbA1c outcomes"* (Linagliptin triple therapy PSD). The PBAC considered that there was insufficient evidence to demonstrate the non-inferiority of linagliptin triple therapy and pioglitazone triple therapy and the submission was rejected.

Without a head-to-head trial, or new trials of pioglitazone triple therapy which could be used in an indirect analysis, the uncertainty around the comparative effectiveness of gliptin triple therapy and pioglitazone triple therapy will remain. The difficulties associated with using indirect analyses are a result of methodological constraints which can not be easily overcome without additional comparable efficacy and safety data. It is unlikely that new trials of pioglitazone triple therapy will be conducted given the reluctance of clinicians to randomise patients to pioglitazone due to its ongoing safety concerns. Similarly, Sponsors are unlikely to conduct head-to-head trials of pioglitazone triple therapy and triple therapy with currently reimbursed drugs or emerging drug classes such as GLP-1 agonists and SLGT-2 inhibitors. This is increasingly unlikely as the use of pioglitazone is declining and few international regulators or payers would consider pioglitazone to be the appropriate key comparator for a new product.

Expanding the number of options for triple therapy would not necessarily be associated with increased costs to the Government. Patients who are intolerant to pioglitazone triple therapy or are concerned about safety issues must be prescribed exenatide if they wish to receive triple therapy under the current PBS restrictions. Exenatide triple therapy is the most expensive third line treatment option listed on the PBS, and allowing patients to choose triple therapy with other classes such as gliptins when this is the preferred treatment option may result in cost savings to the Government.

Barriers to new PBS listings for combination treatment with insulin

Pioglitazone is the only third line diabetes product reimbursed for use in combination with insulin. Clinicians have no alternative options if combination therapy with insulin is the most appropriate treatment for their patient.

Saxagliptin and dapagliflozin were both rejected for this indication, dapagliflozin at the March PBAC 2012 meeting and saxagliptin at the July 2012 PBAC meeting. One of the key reasons for the rejection of these submissions related to methodological issues associated with indirect analyses between the gliptins and pioglitazone. These were similar to the issues identified for the linagliptin triple therapy submission. These include limitations with the pioglitazone plus insulin trial data, such as difference between pioglitazone doses in the trials (15 mg and 30 mg) and the pioglitazone doses used in Australia (15 mg, 30 mg and 45 mg). Without new 45 mg pioglitazone trials which could be included in an indirect analysis, or new head-to-head trials, the comparative efficacy of new products and 45 mg of pioglitazone can not be established. Similarly, there were differences in the dose of insulin used in the trials which could suggest that indirect analyses were inappropriate. These issues were highlighted by the PBAC, which noted that *"differences between the trials in terms of insulin dose (protocol driven regimen versus investigator's discretion), diabetes management (use of rescue medication and definitions of hypoglycaemia), and concomitant metformin use in Trial CT-057 add more uncertainty to the indirect comparison results."* (Saxagliptin plus insulin PSD July 2012) and *"that there were substantial differences in the treatment of the comparator arms between the dapagliflozin and pioglitazone trials giving additional uncertainty to the indirect comparison."* (Dapagliflozin plus insulin PSD March 2012).

As discussed above, it is unlikely that new trials or new head-to-head data will be generated for this indication given the ongoing pioglitazone safety concerns. The difficulties associated with using indirect analyses can not be easily overcome without additional comparable efficacy and safety data. Consequently, the uncertainty around the comparative effectiveness of gliptins and pioglitazone when used in combination with insulin will remain. It

is therefore unlikely that any products will be able to achieve a PBS listing for this indication, despite the clinical need for alternative treatment options.

Barriers to new PBS listings for fixed dose combinations

The requirements for PBAC submissions for fixed dose combinations (FDCs) have become increasingly rigorous. The first two DPP-4 and metformin FDCs listed on the PBS were considered minor submissions (sitagliptin with metformin, March 2009 PBAC meeting, and vildagliptin with metformin, November 2010 PBAC meeting). However, the PBAC requested a major submission for linagliptin with metformin in order to be considered at the March 2013 PBAC meeting.

The linagliptin with metformin and saxagliptin with metformin FDCs were both deferred at the March 2013 PBAC meeting pending finalisation of the TGA registration. The documentation available for the linagliptin FDC had previously been considered as sufficient TGA documentation for the PBAC to make a decision for other submissions evaluated under the TGA-PBAC parallel processes. These new barriers to PBAC decision making may delay PBS listing timelines and ultimately patient access to new medicines.

The linagliptin and saxagliptin FDCs were also delayed pending consideration of an analysis of utilisation data conducted by the Drug Utilisation Sub-Committee (DUSC). The data was considered at a special, out of session meeting of the PBAC in April 2013. Subsequently, the FDCs were recommended for listing at a lower price than proposed by the Sponsors and with a modified restriction. There are a number of concerns around the appropriateness of the PBAC basing decision making on the DUSC analyses prior to the conclusions of the Diabetes Review, which are discussed in further detail on page 10.

Improving patient access

Currently, the third line diabetes drug with the broadest indication is also associated with the greatest safety concerns. Newer medicines have not successfully achieved a PBS listing for these indications. This is predominantly due to the methodological limitations associated with indirect analyses. While it would be ideal to conduct head-to-head trials of new medicines and pioglitazone, this is unlikely to occur due to the safety concerns associated with pioglitazone. Australia is a small market and the PBAC is one of the few payers which has identified pioglitazone as a key comparator.

It is difficult to achieve a positive PBAC recommendation when the main consideration for determining non-inferiority is based on the primary outcome alone. Given the differences in trial design it may be appropriate to consider a broader range of clinical outcomes. Although reduction in HbA1c is a clinically relevant outcome, other outcomes such as proportion of

patients achieving an HbA1c level less than 6.5% and safety outcomes such as episodes of hypoglycaemia are also important. The clinical need for alternative treatment options should be considered when there is limited clinical trial data or a small degree of uncertainty in the indirect analyses.

It should also be noted that expanding the list of reimbursed indications for currently listed products will not necessarily be associated with additional costs to Government. Broader indications would be based on a cost-minimisation argument. In fact, allowing patients to receive oral treatments in preference to injectable drugs may be associated in cost savings to Government.

Given that the barriers to achieving a PBS listing are likely to remain, Boehringer Ingelheim requests that the PBAC considers the criteria used to assess new diabetes products and indications and considers the broader clinical need for alternative treatment options.

Consolidation of all relevant clinical trial evidence

The third Term of Reference for the Review is to consolidate the clinical trial evidence used to support PBS listings of diabetes medicines listed since 2002. However, it is not possible to adequately address this in the time provided by the Department. Consolidation of all clinical trial evidence used to support PBS listings would require reviewing a substantial number of clinical trials. It is not clear what the purpose of this consolidation would be given that each trial has already been considered by the PBAC. While it could be informative to perform a comparative analysis of these trials for all drugs and indications, this is a significant amount of work which could not be performed in the six week time frame given for submissions to the Diabetes Review. In addition, the clinical trials selected for inclusion in individual PBAC submissions are not representative of the complete clinical trial evidence for each drug. PBAC submissions select one or two comparators and only include trials which can be used to compare with these key comparator. Care must therefore be taken when interpreting this data as it comes from a selected set of trials.

The fourth Term of Reference relates to the identification of any clinical trials and meta-analyses for PBS listed drugs which have not been previously considered by the PBAC. It is appropriate for the PBAC to consider additional trials given the limitations of only evaluating clinical trial data used to support PBS listings. However, conducting a systematic literature review to identify all additional clinical trials of every PBS listed drug and collating this data is simply not feasible within a six week time frame. The National Health and Medical Research Council (NHMRC) handbook for reviewing scientific literature (NHMRC 2000) noted that showed that the average time spent by a specialist company in conducting a systematic

review was 1,139 hours (approximately 30 person-weeks of full-time work), ranging from 216 hours to 2,518 hours (6 person-weeks to 67 person-weeks). A review of all literature for all PBS listed diabetes medicines would be at the upper end of this range given the substantial number of medicines and indications currently available.

Undertaking a literature review of this scope requires clearly defined objectives. The aim stated in the Terms of Reference, to collate and evaluate additional evidence, is broad and undefined. It provides no guidance as to the specific questions to be addressed, which is a critical component of conducting a systematic review (NHMRC, 2000). It is stated that all trials that would inform the consideration of the PBAC should be included. However, it is unclear what trials would be informative to the PBAC given that the aims of the Diabetes Review are not clearly given, therefore it must be assumed that all trials not previously considered by the PBAC are to be identified and reviewed. The level of evidence for these trials is not stated, therefore randomised controlled trials through to case studies could be included. This significantly increases the work required to adequately address this Term of Reference. To illustrate the scope of this request, a basic literature search was conducted in Embase (see Appendix 1). The MeSH term for each drug was used, with the requirement that it be the focus of the article. No keyword searching of abstracts and titles was included. This was a conservative search strategy. It should be noted that a standard search used in a PBAC submission would typically be much broader, in addition to including multiple databases including Medline and the Cochrane Library. Nevertheless, the Embase search identified over 16,000 abstracts published since 2002. It is estimated that developing inclusion and exclusion criteria for the articles, reviewing all abstracts, retrieving full text articles, reviewing the articles and identifying relevant trials would take over two months. This is before any critical appraisal of the included trials has been undertaken. Appropriately evaluating this body of evidence both within drug classes and between drug classes is a further significant piece of work. The most informative analysis of this data would involve multiple indirect analyses or network meta-analyses, and it is not unreasonable to expect the full process to take well over a year given the estimates cited in the NHMRC handbook (NHMRC, 2000). It is unclear if the Diabetes Review has sufficient resources or time to conduct this type of analysis, nor what the intended outcome of reviewing this additional evidence would be. The magnitude of this request is such that this work can not be completed within the timelines provided for the Diabetes Review.

It is appropriate that the evidence used by the PBAC to make decisions during the Diabetes Review be of the same level and quality as the evidence required for a PBAC submission. That is, systematic reviews of the literature, comparative analysis of efficacy and safety outcomes against relevant comparators, and a cost minimisation or cost effectiveness

analysis. It would be inconsistent to make decisions regarding the current PBS listing of products based on a highly selected and potentially biased set of data, while rejecting submissions for new diabetes drugs and indications due to lack of data meeting strict PBAC criteria.

Utilisation patterns and current PBS restrictions

The DUSC conducted an analysis of PBS and RPBS data to evaluate utilisation patterns for diabetes medicines. One interpretation of the data is that a proportion of patients are prescribed diabetes products outside of PBS restrictions. Care must be taken when analysing prescribing data, particularly when identifying patients on multiple medications or patients switching between medications. Patients rarely finish a full course of their previous medication at the time they are prescribed a new treatment regimen if they present with adverse effects or if their diabetes remains uncontrolled. There is generally a period of overlap between the treatments and, therefore, a treatment switch (moving from drug A+B to drug C) and co-administered treatment (moving from drug A+B to drug A+B+C) must be carefully defined. The definitions used in the DUSC additional analyses report are inconsistent. A treatment break was defined as no treatment for two standard coverage days (the median time to re-supply for all prescriptions) or two months. Patients who received two drugs concurrently for five or less weeks were considered to have switched from the first drug to the second drug, while patients who received two drugs concurrently for six or more weeks, were considered to be co-administered both drugs. The six week cut-off is an arbitrary definition, with patients who had two or more packs of drug remaining at the time of a treatment switch being misclassified as having co-administered drugs. Simons *et al* 2011, Calcino *et al* 2010 and Ortiz *et al* 2010 defined co-administration as scripts for both molecules in two consecutive months, and switch as only one month with both scripts or no overlap. These definitions provide more confidence that the patient is accurately defined as receiving co-administered therapies. Other methodological issues are the calculation of treatment regimen on a weekly rather than daily basis, given that most prescriptions are for a month's supply. Furthermore, calculation of treatment breaks did not take non-compliance into consideration. The methodology used in the DUSC analyses is likely to have overestimated the proportion of patients who were identified as being inappropriately prescribed diabetes medicines.

The PBAC should consider why some clinicians may be prescribing diabetes drugs inappropriately. The DUSC has suggested that the current wording of the PBS restrictions for diabetes products is complex and could be simplified. Some clinicians may not prescribe diabetes medications in accordance to PBS indications due to misinterpretation of the

restrictions or due to individual patient characteristics or due to more relevant treatment guidelines than PBS restrictions. The RACGP treatment guidelines provided limited guidance as to the use of combination treatments, recommending that clinicians make treatment decisions based around drug class rather than dual vs triple therapy options. Improvements to the restriction could include clarifying the wording of the listings and representing the treatment algorithm graphically. This is consistent with international treatment guidelines, such as the International Diabetes Federation (IDF 2012) and the joint Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Inzucchi *et al* 2012). Changing the PBS restrictions so that clinicians have a clear understanding of how the PBAC intended the products to be prescribed may reduce the proportion of patients who receive diabetes products inappropriately. Boehringer Ingelheim supports modifications to the current restrictions as long as this does not reduce patient access to medicines.

The clinical need for alternative treatment options is also likely to be driving some inappropriate prescribing patterns. For example, if a proportion of patients are receiving gliptin triple therapy then it is feasible that some clinicians are aware that this treatment combination is not reimbursed but choose to prescribe these drugs in preference to reimbursed treatment options based on patients' characteristics and needs. There are a number of limitations associated with the reimbursed triple therapy treatment options, pioglitazone and exenatide, including safety concerns, contraindications, preference for oral treatment options and additional costs. Ensuring that a full range of clinically and cost-effective treatment options are available to patients may reduce inappropriate utilisation, improve diabetes control rates and reduce diabetes complications.

Outcomes of the PBAC review

The primary aim of the Diabetes Review should be to ensure that patients have access to necessary treatment options and are using these drugs in line with the registered and reimbursed indications. This should represent both clinical and cost effective use. It is important that reviews are aligned with the National Medicines Policy and develop recommendations which are consistent with the principles of quality use of medicines. The intent of the review should not to be to reduce the costs associated with listing drugs on the PBS. Furthermore, cost savings should not be expected to be an outcome of reviewing PBS listed drugs, and it is concerning that cost savings resulting from reviews have been forecast in the 2011-2012 Commonwealth budget. It is clear from the 2013-14 Budget that the Government is using post-market surveillance and reviews as a mechanism to generate savings to the PBS. One recent example is market review of medicines used in the

treatment of Alzheimers Disease which the Budget papers have noted will generate savings of $55.7 million over five years.

The Diabetes Review should not delay patient access to new medicines. However, the listing of two new gliptin FDCs may have been delayed. At a special April 2013 PBAC meeting it was recommended that both of these products be PBS listed at a significantly lower price than the combined price of the two individual components. This was based on the DUSC analyses, despite the fact that the DUSC analyses have yet to be considered or validated by the PBAC as part of the Diabetes Review. In effect, the PBAC is seeking to pre-empt the conclusions of the Review. The PBAC stated that, *"From the findings of the DUSC utilisation analysis.... a significant proportion of patients initiated on a regimen containing a gliptin + metformin FDC had been supplied only metformin as pre-initiation...[and] ...recommended listing of the [linagliptin or saxagliptin] + metformin FDC on a cost-minimisation basis with the individual components for the proportion of use previously determined to be cost-effective, and on a cost minimisation basis with metformin plus the average daily dose of a sulfonylurea for the proportion of use where cost-effectiveness has not been established"* (April 2013 PBAC outcomes). While the DUSC analysis forms part of the Diabetes Review, to base any PBAC decision on this data before the Diabetes Review has concluded is premature at best. It is uncertain how the April PBAC recommendation will be affected once the Government's Review is completed. The Diabetes Review should not implement recommendations which reduce the treatment options currently available to doctors and patients.

The first Term of Reference for the Diabetes Review describes the utilisation and patterns of treatment of PBS listed drugs for T2DM, and compares these with PBS restrictions. It appears that the recent PBAC recommendations for the new gliptin FDCs ignore the aim of the Review, which has been tasked to evaluate utilisation of medicines used in the treatment of type 2 diabetes, including the gliptins. The PBAC recommendation for the new gliptin FDCs again highlights the cost saving intention of the review processes.

It is important that Sponsors are not penalised for utilisation patterns that the DUSC and PBAC deem as inappropriate. Sponsors are only the stakeholders in the treatment of type 2 diabetes patients. Clinicians base their treatment decisions on guidelines and individual patient characteristics. The RACGP guidelines provide no clear recommendations on the use of combination therapy, with no guidance given for dual therapy, triple therapy or the use of FDCs. The guidelines indicate that prescribers should first choose the class of drug which is most appropriate and then allows each prescriber to decide the appropriate combination of treatments. In this context the choice of dual therapy compared with triple therapy is less important than the choice of a gliptin compared with a glitazone, and it is perhaps not

surprising that clinicians prescribe treatment combinations not currently PBS listed. It is clear that prescribes see the clinical need for more treatment options and Sponsors should not be penalised with price reductions as a result of this. Requesting that Sponsors reduce the price of medicines on the basis of clinicians prescribing drugs outside of PBS restrictions does not alter the underlying issue of inappropriate prescribing. It is important that any inappropriate drug use is also addressed through other mechanisms given that the main aim of the Diabetes Review should be to ensure that drugs are used in line with PBS restrictions. This could include strategies such as implementing clinical education programs to reinforce PBS restrictions. It may also be that inappropriate utilisation reflects a high unmet clinical need. As discussed previously, there are few options for clinicians wishing to prescribe triple therapy with metformin and sulfonylurea or combination therapy with insulin. Those limited options may not be appropriate for some patients. The PBAC should also consider if other approaches, such as a clearer representation of the treatment algorithm in the PBS listing, would reduce the proportion of doctors who prescribe diabetes medicines outside of the PBS listing.

The Diabetes Review should be an extension of the high quality, rigorous and transparent evaluation process which occurs when the PBAC consider submissions for new drugs and indications. However, there is little information or methodology provided regarding the level of detail required for submissions and how the evidence and analysis conducted for the review reflect the actual outcomes. It is unclear how submissions to the Diabetes Review will be incorporated into the review process and to what extent they influence decision making. It would be of benefit to have the framework for the review process more clearly defined and publically available. It is also important that Sponsors are given adequate notice of recommendations arising from reviews and sufficient time to implement changes.

Conclusions

The primary aim of the Diabetes Review should develop evidence based recommendations. It would be inappropriate to apply less rigour to outcomes resulting from post market reviews than is applied during the assessment of new medicines. However, is it unclear how the Terms of Reference for the Diabetes Review will be addressed and how the evidence and analyses considered in the review will be used to develop recommendations. The processes for conducting post market reviews need to have increased transparency and certainty. In addition, the scope of the Diabetes Review is simply too large for Sponsors to provide appropriate input in the six week timeframe provided. It is also unclear if the Government have allowed sufficient time and resources to adequately address the Terms of Reference.

From previous reviews and FDC recommendations it is clear that the aim of the Government is to seek price reductions. Sponsors should not be penalised for prescribers seeking additional treatment options outside of current PBS restrictions, particularly when price reductions do not alter clinician treatment patterns. Cost savings should not be the primary aim of post market reviews. The main outcome of the Diabetes Review should be to ensure that patients have timely access to range of clinically and cost effective diabetes medicines.

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Appendix 1

A literature search was conducted using the Embase database on 4th June 2013. The results are shown in Table 1. The MeSH terms for each of the diabetes drugs identified in the Diabetes Review was used, with the focus option selected in order to be conservative. A total of 16,363 citations were identified.

Table 1 Embase search strategy

	Search terms	Number of citations
1	*metformin/	7,495
2	*glipizide/	706
3	*gliclazide/	853
4	*glibenclamide/	3,349
5	*glimepiride/	727
6	*acarbose/	1,235
7	*rosiglitazone/	3,187
8	*pioglitazone/	2,992
9	*linagliptin/	204
10	*saxagliptin/	247
11	*sitagliptin/	865
12	*vildagliptin/	427
13	*glucagon like peptide 1/	2,969
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	21,817
15	limit 14 to yr="2002 -Current"	16,363