Introduction

Servier Laboratories (Servier) is the sponsor of Diamicron MR (gliclazide 60mg modified release tablet), currently listed on the PBS as an unrestricted item on the General Schedule of the Pharmaceutical Benefits Scheme (PBS).

Servier has noted with interest the outcomes of the Drug Utilisation Subcommittee (DUSC) reviews of utilisation of medicines in type 2 diabetes (October 2012 and February 2013) and the Pharmaceutical Benefits Advisory Committee (PBAC) views in relation to these outcomes, as outlined in the minutes of the April 2013 Special PBAC Meeting.

The current submission represents a brief response to the views expressed in the PBAC minutes, addressing Terms of Reference 1-4 of the Review of Medicines Used in the Treatment of Type 2 Diabetes. While much of the information referred to in the submission will be familiar to the PBAC, Servier believes there is additional evidence to be central to the issues being considered and should therefore be assessed equally alongside data relating to utilisation and cost effectiveness.

Gliclazide MR clinical background

Gliclazide modified release (MR) is a once daily formulation of the sulfonylurea gliclazide. It was included on the PBS in June 2001 on a cost minimisation basis compared to immediate release gliclazide.

In December 2001, following the presentation of detailed clinical and cost-effectiveness data, PBAC agreed that gliclazide had been demonstrated to cause less hypoglycaemia than an alternative sulfonylurea, glibenclamide, and that a small price premium represented acceptable cost effectiveness.

The Phase III program for gliclazide MR included a relatively unrestricted population of 1,462 type 2 diabetic patients, followed for up to 10 months. Results with the modified release formulation were entirely consistent with those obtained with gliclazide immediate release, the long term efficacy and safety of which had been previously demonstrated in a five year prospective randomised trial (Harrower, 2000); (Gillauseau, 1991).

Since the development and availability of gliclazide MR, a strong body of evidence has also been amassed, which demonstrates the favourable efficacy, safety and tolerability profile of the drug in comparison to other oral anti-diabetic agents.

In the ADVANCE trial, 11,140 patients with type 2 diabetes were randomised to undergo either standard glucose control or intensive glucose control (defined as the use of gliclazide MR plus other drugs as required to achieve an HbA1c ≤6.5. After a median of 5 years of follow up, the mean HbA1c was lower in the intensive control group than in the standard control group. Importantly, intensive control with gliclazide MR-based therapy reduced the incidence of combined major macrovascular and microvascular events as well as that of microvascular events alone (Patel, et al., 2008). Such data is still lacking for other sulphonylureas with the exception of glibenclamide, and for the newer agents, which is a focus of the DUSC review.

The favourable safety and tolerability profile of gliclazide MR has been highlighted in the European GUIDE study. In this study, 845 type 2 diabetic patients were randomised to either gliclazide MR or glimepiride daily, as monotherapy or in combination with their current treatment, according to a 27 week, double blind design. HbA1c levels decreased similarly in both groups, but hypoglycaemia occurred significantly less frequently in the gliclazide MR group, with approximately 50% fewer confirmed hypoglycaemic episodes occurring in this group (Schernthaner, et al., 2004).

The low risk of hypoglycaemia with gliclazide has been confirmed in two separate studies in diabetic patients fasting for Ramadan. In both studies, patients taking gliclazide had a markedly lower rate of hypoglycaemia than those taking other sulphonylureas. Furthermore, the hypoglycaemic rate with gliclazide in each study was numerically lower than that for sitagliptin, a DPP4 inhibitor. (Al Sifri et al, 2011; Aravind SR, 2012).

Potentially important clinical benefits of gliclazide MR have also been identified in observational studies. One analysis based on the French registry of Acute ST elevation and non-ST elevation Myocardial Infarction (FAST-MI) found that mortality was significantly lower in patients previously treated with sulphonylureas compared to those on other oral medications, and that among SU-treated patients, in-hospital mortality was lower in patients receiving gliclazide or glimepiride compared with glibenclamide (Avogaro, 2012); (Zeller, et al., 2010).

Another retrospective study, undertaken at a single centre in Japan, explored secondary sulphonylurea failure and time to insulin therapy in 274 patients. This study found that the periods until the start of insulin treatment from diabetes onset, diabetes treatment, or initiation of treatment with gliclazide or glibenclamide, was significantly longer in the gliclazide group than those in glibenclamide group (Satoh, et al., 2005).

Australian and international guidelines

Reflective of the well established evidence base and long real world clinical experience of sulphonylurea therapy in type 2 diabetes, and the favourable efficacy and safety profile of glicliazide MR treatment in particular, local and international guidelines continue to place these agents as the second line therapy of choice, behind first line treatment with metformin.

The International Diabetes Federation guidelines for second line therapy in type 2 diabetes state that: "When glucose control targets are not being achieved, add a sulfonylurea. Other options include adding metformin if not used first-line, an a-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor or a thiazolidinedione. A rapid-acting insulin secretagogue is an alternative option to sulfonylureas" (IDF, 2012).

Australian therapeutic guidelines state that: "Metformin is the oral anti-diabetic drug of first choice in type 2 diabetes. If glycaemic targets are not met with maximal tolerated doses of metformin then it is common to add a sulfonylurea, a practice that is supported by decades of clinical experience. If this dual oral therapy approach is unsuccessful, insulin therapy should preferably be added to this regimen as it is highly effective. Other options for therapy include thiazolidinediones, acarbose, incretins and glitinides." (www.etg.org).

The Australian guidelines add that: "sulfonylureas vary in their propensity to cause hypoglycaemia—glibenclamide more commonly causes this adverse effect. Longer-acting sulfonylureas (glibenclamide and glimepiride) should usually be avoided in older people with type 2 diabetes because the risk of these drugs causing severe prolonged hypoglycaemia is increased, especially in people with deteriorating renal function." (www.etg.org).

Options being considered by the PBAC

At the April 2013 Special Meeting, PBAC considered results of the DUSC review of the utilisation of medicines for diabetes in Australian clinical practice. The Committee agreed with DUSC that there appears to be extensive use of currently approved third-line agents (gliptins, glitazones and exenatide) beyond their PBS restrictions and that this is particularly pronounced among fixed dose combination (FDC) products. Servier does not dispute this conclusion, which is consistent with its own understanding of the dynamics of the current Australian type 2 diabetes market.

In seeking to address the use of more expensive third-line agents beyond their current PBS restrictions, PBAC considered a number of potential actions, including prescriber education, amending restrictions, introducing telephone authorities for diabetes FDC products and recommending renegotiating the price of FDCs based on their actual place in therapy (with potential flow on effects to the component single agents). Furthermore, the PBAC recommended that the restrictions for the gliptin FDC products be amended to remove the requirement for a patient to be intolerant to a sulphonylurea (contingent on a price reduction or demonstration of acceptable cost effectiveness).

Based on the information provided in the minutes of the April 2013 Special Meeting, at this stage of the review process, it appears that PBAC is mostly concerned with ensuring that current utilisation of PBS listed diabetes medicines represents expected cost effective use, which evidence from the DUSC review suggests may not be the case.

Servier strongly believes that this concern regarding cost-effectiveness should be weighed equally with concern as to whether current utilisation patterns represent clinically appropriate use. Extensive clinical experience, long term randomised controlled trial data and therapeutic guidelines, all strongly support the place of sulphonylureas (and shorter acting agents such as glicliazide MR in particular) as the second line treatment of choice in type 2 diabetes.

Some of the actions being considered by PBAC in search of more cost effective use of newer classes of diabetes medicines (i.e. relaxed restrictions accompanied by reduced prices) are likely to accelerate the substitution of these agents into second-line therapy, even where clinical data supporting such substitution is mixed or lacking and evidence based treatment guidelines continue to support sulphonylureas as the second line agent of choice.

While fully recognising PBAC's desire to ensure that existing and emerging type 2 diabetes medicines are used in a cost effective manner in Australian clinical practice, Servier believes this may be better achieved through initiatives aimed at optimising the use of established, inexpensive, evidence based second line treatment options, such as gliclazide MR and other sulphonylureas, than by further expanding access to newer agents such as gliptins, GLP1 agonists, and glitazones.

Conclusion

Servier values the opportunity to contribute to this stage of the Review of Medicines Used in the Treatment of Type 2 Diabetes, and looks forward to reviewing its outcomes and contributing to subsequent stages of the process as appropriate.

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