New Medicine Report | Gliclazide MR
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Document Status | Post D&TC
Traffic Light Decision | Double Green
Date of Last Revision | 29th March 2004
Approved Name | Gliclazide MR
Trade Name | Diamicron MR™
Manufacturer | Servier
Legal Status | POM
Indication | Non insulin-dependent diabetes in adults where dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose
Dosage | 30mg daily increasing if necessary to 120mg daily – to be taken in the morning
Cost | £4.00 for 28 tablets
Possible Number of Suffolk Patients | Not calculated
Number Needed to Treat | Not calculated
Treatment Alternatives | Gliclazide £2.58 for 28 tablets of 80mg
Gliclazide £6.05 for 60 tablets of 80mg
Diamicron £7.00 for 60 tablets of 80mg
NB gliclazide 80mg tablet equivalent to gliclazide 30mg MR
Glimepiride
Other oral hypoglycaemics
Future Alternatives | None known
Possible Future Indications | None known

Reviewer’s Comments

Gliclazide MR is a new presentation of an established treatment for Type 2 diabetes.

It would appear to have no advantage in controlling either HbA₁c or fasting plasma glucose levels over the standard preparation.

Where compliance with treatment is of concern then reducing the frequency of dosing to once a day may be helpful in maintaining control and this product would be of use in such circumstances.
Evidence Reviewed

<table>
<thead>
<tr>
<th>Paper, Review, Abstract etc.</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drouin P &amp; the Diamicron MR study Group, Diamicron MR once daily is effective and well tolerated in type 2 diabetes – a double-blind, randomised, multinational study J of diabetes &amp; its complications;2000:14:185-191</td>
<td>I</td>
</tr>
<tr>
<td>NICE Management of Type 2 diabetes – Management of blood glucose</td>
<td>III</td>
</tr>
<tr>
<td>Chesterfield Royal Hospital New product review</td>
<td>III</td>
</tr>
<tr>
<td>Information provided by Servier</td>
<td>IV</td>
</tr>
</tbody>
</table>

Level of evidence adapted from “Quick and Clean”: authoritative health technology assessment for local health care contracting Andrew Stevens, Duncan Collin-Jones & John Gabbay Health Trends Vol 27 No 2 1995

Submitted for comment to: Medical Information Department, Servier 24.02.04

Dr G Rayman, The Ipswich Hospital
Dr Parkinson, The Ipswich Hospital
Dr Fowler, The Ipswich Hospital
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Dr N Huston, James Paget Hospital

Review

This review is written from a starting point that there is no doubt about the efficacy of gliclazide in the treatment of non insulin-dependant diabetic patients. Thus the review will consider the evidence for equivalence between standard gliclazide and gliclazide MR and the latter’s place in therapy.

The new MR product contains a hydrophilic matrix of fibres holding gliclazide in place. Following ingestion some gliclazide is released immediately and other fibres soften to ensure a gradual supply of active ingredient through the day. Levels of gliclazide are therapeutic throughout the day but relatively reduced during the night-time period which is thought to help reduce the risk of nocturnal hypoglycaemia. Bioavailability of gliclazide is said to be 97% in the MR formulation compared to 40-80% with the standard tablet. It is suggested that a 30mg dose of the MR formulation is thus equivalent to 80mg of the standard formulation. This is investigated by Drouin below.
Drouin reports a double-blind, multicentre study into the long-term efficacy and safety of gliclazide MR compared to gliclazide. Patients with Type 2 diabetes for at least 6 months were eligible to enter the study. Following a 2-week washout period with no oral hypoglycaemic treatment inclusion criteria for the remainder of the study included glycated haemoglobin level between 6% and 9% and a fasting plasma glucose (FPG) level between 7.8 and 13.9 mmol/l.

Patients with Type 1 diabetes, Type 2 but requiring insulin, ketosis and ketoacidosis were excluded, as were patients with a history of allergy to sulfonylureas and other acute or chronic diseases known to affect glucose control. Patients with evidence of hepatic or renal disease (defined as transaminases or alkaline phosphatases more than 3 times the upper limit of normal or a plasma creatinine level above 150 mmol/l) or who were pregnant or breastfeeding were also excluded.

Following the initial 2-week drug free period patients were randomised to either treatment with standard gliclazide 80mg (N=399) or gliclazide MR 30mg (N=401). Over the next 4 months patients were titrated to a dose necessary to achieve an FPG between 4.4 and 6.6 mmol/l for patients under 65 and between 5.5 and 7.7 mmol/l for patients 65 and above. The MR dose was given once in the morning and the standard dose was given twice a day with the exception of the 80mg dose which was given in the morning. All patients received placebo tablets as necessary to protect the blinding. At the end of the titration period patients were then entered into a 6 month fixed dose treatment period. At the end of this period patients in the gliclazide group were switched to gliclazide MR during a single blind phase which continued for a further 2 months.

The results showed that gliclazide MR was significantly non-inferior to gliclazide in terms of efficacy for both HbA1c (p=0.001) and FPG (p=0.001). The secondary efficacy criteria showed no clinically relevant differences after 10 months. The mean fasting insulin level and triglycerides, total cholesterol and HDL cholesterol levels remained stable in both groups.

The ability to switch from gliclazide to gliclazide MR was assessed at the end of the 10-month period. Metabolic control remained stable and comparable between the groups for the next two months.

Adverse Effects etc.

In the study by Drouin 46.9% of the patients in the gliclazide MR group and 50.3% of patients in the gliclazide group reported adverse events. The most frequently reported events were arthralgia (3.4%), arthritis (2.8%), back pain (3.4%) and bronchitis (4.9%) with a similar frequency in both groups. There were four cases of serious adverse events in the gliclazide group (vision disorder, GI disorder, hyperglycaemia and hypertension) and one serious adverse event (malaise) in the gliclazide MR group.
The numbers of episodes of hypoglycaemia are shown in Table 1

Table 1
To show the frequency of episodes suggestive of hypoglycaemia

<table>
<thead>
<tr>
<th>Number of episodes of hypoglycaemia per 100 patients months</th>
<th>Gliclazide MR</th>
<th>Gliclazide (standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Whole study population</td>
<td>401</td>
<td>1.2</td>
</tr>
<tr>
<td>Elderly ≥65 years</td>
<td>147</td>
<td>0.2</td>
</tr>
<tr>
<td>Patients previously managed by diet alone</td>
<td>81</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Twenty-one (5.2%) of patients in the gliclazide MR group and 16 (4%) in the gliclazide group experienced symptoms of hypoglycaemia all of which were mild to moderate with the exception of one patient in the gliclazide group who required assistance. It is of interest to note the low frequency of hypoglycaemia in patients ≥65 years of age 45% of whom had impaired renal function. The SoPC for the product recommends that regular food intake, including breakfast, should be maintained throughout the day.

Health Economics

Type 2 diabetes affects an increasing number of people in the UK. The serious complications which can arise place a burden on both the patient and relatives and the NHS.

Many of the complications can be prevented, delayed or limited by good management of the condition.

Compliance with the medication regimen is accepted as an important part in the good management of disease.

It can be argued that where compliance is a problem reducing the number of medications or the frequency at which they are taken may improve the patient’s adherence to the regimen. Thus the introduction of a once daily medication may be of benefit in this group of patients. There is, however, some debate about whether reducing dosage from twice daily to once daily is effective and many compliance schedules are aimed to reduce the frequency from three or four times a day to twice a day.
Response from Servier

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4 March 2004
01753 666218
01753 666204

Dear Mr Evans

Re: Diamicron MR (gliclazide)

Thank you for sending me the New Medicines Report on Diamicron MR (gliclazide) for the Suffolk Drug & Therapeutic Committee and requesting my comments on this report.

I have two comments to make on this report. Firstly, as glimepiride is mentioned as an alternative treatment I think it is important to note that in a large, randomised controlled trial involving a total of 845 type 2 diabetic patients, which compared Diamicron MR once daily to glimepiride once daily, it was reported that patient assigned to Diamicron MR experienced 50% less hypoglycaemic episodes that patients assigned to glimepiride1.

Secondly, I would like to respond to your comments about the effectiveness of reducing dosing of antidiabetic medication from twice daily to once daily. The retrospective cohort study, by Donnan et al, of 2,920 patients prescribed oral hypoglycaemic drugs for at least 12 months found that there was a significant linear trend of poorer adherence with each increase in the daily number of sulphonylurea tablets taken (p = 0.001). Donnan et al concluded that one tablet per day administration was associated with greater adherence than multiple tablets2.

Once again thank you for providing me with the opportunity to make comments on the report. I trust that this information is useful. Please contact me if you require anything further.

Yours sincerely
For SERVIER LABORATORIES LTD

Dr Emma Sherrington D. Phil
Medical Information Officer
External Relations & Regulatory Affairs Department

References:

1. *Schernthaner G et al
   The European GUIDE–study: Head-to-head comparison of efficacy and safety of two once daily sulphonylureas gliclazide MR and glimepiride in 845 Type 2 diabetic patients
   18th International Diabetes Federation Congress August 24-29 2003; Paris, France: PS 62 Insulin Secretagogues
2. *Donnan P T
   Adherence to prescribed oral hypoglycaemic medication in a population of patients with type 2 diabetes: a retrospective cohort study
   Diabetes & Metabolism 2002; 19: 279-284

12 March 2004
01753 666218

01753 666204

Dear Mr Evans

Re: Diamicron MR (gliclazide)

Thank you for sending me the New Medicines Report on Diamicron MR (gliclazide) for the Suffolk Drug & Therapeutic Committee and requesting my comments on this report. I understand that the meeting has now been postponed until the 24 March. Therefore, I would like to take this opportunity to provide you with some additional information that has only recently become available.

Further to my earlier letter of 4 March 2004, I would like to bring to your attention some additional information regarding the effectiveness of reducing dosing of antidiabetic medication from twice daily to once daily. Guillausseau 2003 reported the results of a prospective assessment of self-reported compliance and its impact on metabolic control in a cohort of 11,896 type 2 diabetic patients treated in general practice. Patients were treated with one or two oral antidiabetic agents. Optimal compliance, i.e., no tablets omitted, was reported in 37% of patients; 46% of patients reported 1-3 omissions per month; 11% of patients reported omissions once a week and 6% reported omissions more frequently than once a month. From multivariate analysis, was found that HbA1c levels were positively correlated with age (r = 0.73 P < 0.0001), daily dosing frequency of oral antidiabetic medication (r = 0.59, P < 0.0001) and low educational level (r = -0.38, P < 0.00001) but not with diabetes duration. It was found that the best metabolic control was achieved with once-daily dosing and HbA1c levels were directly correlated with compliance with treatment (P < 0.01)1.

These results confirm that daily dosing frequency is a modifiable factor that influences compliance. Therefore, as a result of the previous study Guillausseau 2004 conducted a follow-up study to determine the impact of modifying the treatment regimen on compliance and glycaemic control (i.e. HbA1c). The doctors who had participated in the previous study restarted educational training with their diabetic patient and optimised patients’ treatment regimen. In total, 4,802 male and female patients participated in this longitudinal follow-up study. Of these patients 4,186 patients were switched from multiple daily dosing to a once-daily sulphonylurea. Of these, 2,160 patients were switched from a multiple daily dosing regimen of gliclazide to the once-daily gliclazide MR formulation. In addition, where appropriate, patients were switched from bi-therapy to monotherapy. This resulted in a decrease in percentage of patients on bi-therapy (43% to 31.5%, P < 0.001) and an increase in the number of patients on monotherapy (57% to 69.5%, P < 0.001)2.

After 6 months of the optimisation of treatment regimens the mean HbA1c for the total patient population had decreased significantly from 7.5 % ± 1.6 % to 6.9 % ± 1.2 % (P<0.0005). For the patients who switched from a multiple daily dosing to a once daily dosing regimen of a sulphonylurea the mean HbA1c decreased significantly (7.5 % ± 1.6 % to 6.9 % ± 1.2 % (P<0.0005). In addition, for patients switching from multiple daily dosing of gliclazide to once daily gliclazide MR formulation HbA1c for decreased significantly (7.4 % ± 1.8 % to 6.8 % ± 1.2 % (P<0.0005). Guillausseau concluded that these results suggest that optimising oral antidiabetic treatment regimens with the use of once-daily preparations can improve long-term glycaemic control in patients with type 2 diabetes2.

Once again thank you for providing me with the opportunity to make comments on the report. I trust that this information is useful. Please contact me if you require anything further.

Yours sincerely

For SERVIER LABORATORIES LTD