Scottish Medicines Consortium

metformin prolonged release tablets (Glucophage SR®) No. (148/04)

Merck Pharmaceuticals

10 December 2004

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and ADTCs on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Metformin (Glucophage SR®) is not recommended for use within NHS Scotland for the treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycaemic control.

Metformin (Glucophage SR) did not demonstrate any benefits in efficacy or side effect profile over the immediate release metformin and is considerably more expensive.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium.

Metformin HCl prolonged release tablets (Glucophage SR®)

Licensed indication under review:

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycaemic control. Glucophage SR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin

Dosing information under review:

Metformin SR 1000mg -2000mg daily in one or two divided doses

UK launch date

January 2005

Comparator Medications

Gliclazide, glimepiride, glipizide, metformin, rosiglitazone, pioglitazone

Cost per treatment period and relevant comparators

Drug	Dose	Cost per day	Cost per month
Metformin SR	**1000-2000mg daily**	**£0.19 - £0.38**	**£5.34- £10.68**
Metformin	500mg - 1g twice daily 5-20mg daily	£0.05 - £0.11	£1.48 - £2.96
Glipizide	80 - 320mg daily	£0.06 - £0.26	£1.80 - £7.20
Gliclazide	1-4mg daily	£0.07 - £0.28	£1.95 - £7.80
Glimepiride		£0.15 - £0.48	£4.12 - £13.52
Rosiglitazone	4-8mg daily	£0.95 - £1.95	£26.60 - £54.60

Summary of evidence on comparative efficacy

Preliminary pharmacokinetic studies found steady-state peak plasma concentrations for prolonged-release metformin were comparable and occurred later (T_{max} 3-5 hours) than with metformin immediate-release. The extent of absorption for the two formulations was similar.

A 24-week, double-blind, randomised, controlled trial, in 217 type 2 diabetic patients (who had been receiving immediate-release metformin 500mg twice daily for at least 8 weeks previously), compared metformin 500mg twice daily (n=71) with metformin prolonged release 1000mg (n=75) and 1500mg daily (n=71). The primary endpoint was the degree of glycaemic control, as determined by the mean change in HbA_{1c} measured from baseline to week 12. Secondary endpoints included mean change in HbA_{1c} at 24 weeks; distribution of HbA_{1c} (<7%, 7-<8% and =8%); measures of blood glucose including changes in fasting plasma glucose (FPG) from baseline and mean daily blood glucose concentrations (self- monitored); fructosamine levels; blood lipid levels; serum insulin levels and body weight at 12 and 24 weeks. Of the 217 patients randomised, 191 patients completed the double-blind phase. Discontinuations were due to patient request (12), adverse events (8), loss to follow-up (3) and other reasons (3). There was no significant difference between treatments in the primary

endpoint; with only small increases in HbA_{1c} in all groups (+0.15%, +0.23% and +0.04% for metformin 500mg twice daily, metformin prolonged release 1000mg and 1500mg daily at 12 weeks and +0.06%, +0.25% and +0.14% at 24 weeks, respectively). No significant differences were found in the secondary efficacy measures of glycaemic control at 24 weeks. However reductions were noted in LDL-C levels, -4mg/dl (95% CI,-9 to 1 in the metformin immediate release group) and -6mg/dl (95% CI, -11 to -1 and -12 to 0 for metformin prolonged release 1000 and 1500mg, respectively). Increases in triglyceride levels in the metformin immediate release group were small (1mg/dl; 95% CI -14 to 7), but increases in both metformin prolonged release groups were statistically significant, 34mg/dl (95% CI, 15 to 53) and 42mg/dl (95% CI, 6 to 78), respectively.

Summary of evidence on comparative safety

The most common adverse effect with metformin is gastrointestinal (GI) disturbance, manifest as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These occur frequently during initiation of therapy and resolve spontaneously in most cases. In addition to the phase lll trial, safety data were available from a retrospective multi-centre, case-control trial of 468 type 2 diabetic patients (metformin immediate release n=158 and prolonged release n=310). The primary outcomes of the study were GI tolerability and frequency of diarrhoea caused by metformin in the two cohorts during the first year of treatment. There was no statistically significant difference in adverse events between the two groups. The relative risk of any GI adverse event for metformin prolonged release compared to immediate release was 1.05 (95% CI: 0.62, 1.78; NS). In the group of patients who switched from metformin immediate release to prolonged release there was a significant reduction in the percentage of patients reporting GI adverse events in the year after switching compared to the year before switching (12% vs 26%, p=0.0006 for at least one GI adverse event and 8% vs 18%, p=0.008 for diarrhoea).

No new safety concerns were raised with prolonged-release metformin that were not known for metformin.

Summary of clinical effectiveness issues

Metformin prolonged release has shown equivalent glycaemic control, as measured by HbA_{1c} to metformin. However, the significant increase in triglycerides noted with the prolonged release formulation but not the immediate release formulation perhaps needs further investigation. The evidence to show that this preparation is better tolerated than metformin is provided mainly by a retrospective, case-control trial in 468 patients.

Summary of comparative health economic evidence

The manufacturer submitted an economic evaluation which shows that (i) Glucophage SR is cheaper than a glitazone and (ii) it is more expensive than a gliclazide. It was not clear why a comparison to metformin had not been made. Glucophage SR is considerably more expensive than metformin.

Budget Impact

The manufacturer estimates that by year 5, metformin SR would save about £30k on the drugs budget based on a comparison with glitazone.

Existing or proposed guidelines and protocols

In November 2001, SIGN produced a guideline for the Management of Diabetes. Guideline No. 55.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 1 December 2004.

Drug prices are those available at the time of SMC assessment.

References

Fujioka K, Pans M, Joyal S. Glycemic control in patients with type 2 diabetes mellitus switched from twice-daily immediate-release metformin to a once-daily extended-release formulation. Clin Ther 2003; 25(2):515-529.

Blonde L, Dailey GE, Jabbour SA, Reasner CA, Mills DJ. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. Curr Med Res Opin 2004; 20(4):565-572.