Scottish Medicines Consortium

Re-submission

Metformin hydrochloride prolonged release 500mg tablets (Glucophage SR®) (No. 148/04)

Merck Pharmaceuticals

9 December 2005

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

ADVICE: following a re-submission

Metformin hydrochloride prolonged-release (Glucophage SR®) is not recommended for use within NHS Scotland for the treatment of adults with type-2 diabetes.

This new formulation appears to have similar short-term efficacy to immediate-release metformin. Evidence of improved gastrointestinal tolerability is not convincing and the prolonged-release formulation is more expensive than the immediate-release formulation.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Metformin 500mg prolonged release tablets (Glucophage SR®)

Indication

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

Dosing information

Starting dose of 500mg once daily, increased as necessary by 500mg increments every 10-15 days to a maximum of 2000mg daily with the evening meal. If glycaemic control is not achieved with 2000mg once daily, 1000mg twice daily should be considered, both doses given with food. If glycaemic control is still not achieved patients may be switched to immediate release metformin up to a maximum dose of 3000mg daily. Patients transferring from immediate to prolonged release metformin should do so at the same equivalent daily dose (up to 2000mg/day).

UK launch date

January 2005

Comparator medications

In the submission, the company do not consider immediate release (IR) metformin as a comparator as they suggest prolonged release formulation should be used for those unable to tolerate the IR formulation. Since the product licence does not restrict the new formulation in this way, metformin IR is included here as a comparator. Other comparators include the sulphonylureas and thiazolidindiones.

Cost of relevant comparators

Drug	Daily Doses	Cost per 28 days	Cost per annum
Metformin SR	**1000-2000mg**	**£5.34-£10.68**	**£70-£139**
Metformin IR	1000-3000mg	£1.45-£4.36	£19-£57
Glipizide	2.5-20mg	£1.48-£7.92	£19-£103
Gliclazide	40-320mg	£0.94-£7.48	£12-£98
Gliclazide MR	30-120mg	£4.40-£17.60	£57-£229
Glimepiride	1-4mg	£4.21-£13.83	£55-£180
Pioglitazone	15-45mg	£24.14-£36.96	£315-£482
Rosiglitazone	4-8mg	£24.74-£49.48	£323-£645

Summary of evidence on comparative efficacy

This resubmission contains details of a study presented in the original submission as well as those of an additional study.

The study presented in the original submission was a 24-week, double-blind, randomised, controlled trial, in 217 type 2 diabetic patients (who had been receiving metformin IR 500mg twice daily for at least 8 weeks previously). This compared metformin IR 500mg twice daily (n=71) with metformin SR 1000mg daily (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. 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 IR 500mg twice daily, SR 1000mg daily and SR 1500mg daily at 12 weeks). At 24 weeks the corresponding changes were +0.06%, +0.25% and +0.14% respectively. No significant differences were found in the secondary efficacy measures of glycaemic control at 24 weeks. However reductions were noted in LDL-cholesterol levels: 4mg/dl in the metformin IR group, and 6mg/dl in metformin SR 1000mg and 1500mg groups respectively. Increases in triglyceride levels in the metformin IR group were small (1mg/dl) but were statistically significant in both SR groups (34mg/dl for 1000mg daily and 42mg/dl or 1500mg daily).

The second publication, new to this resubmission, comprised two separate protocols which compared the change in glycaemic control with metformin SR to placebo. In Protocol 1, 240 type 2 diabetic patients with hyperglycaemia despite diet and exercise were initially randomised to receive metformin SR (500mg daily for week 1, then 1000mg daily thereafter) or placebo once daily for 12 weeks. Patients in the active group with HbA_{1C} >7% and <8% after 12 weeks of treatment then received an additional 500 mg of metformin SR for a further 12 weeks (total of 1500mg daily); those with HbA_{1C} ≥ 8% were withdrawn. The treatment differences in HbA_{1C} between metformin SR 1000 mg once daily and placebo were -0.7% at 12 weeks (primary endpoint) and -0.8% at 24 weeks. After 12 and 24 weeks of therapy, 29% and 35% respectively of metformin SR 1000mg daily treated patients achieved HbA_{1C} < 7% compared with 14% and 11% respectively in the placebo group. Changes in fasting blood glucose were similar to changes in HbA_{1C}. There were no significant effects on lipid parameters at week 12. However, at 24 weeks, LDL-cholesterol was significantly reduced in the metformin SR group compared to placebo (mean change versus placebo –9.0mg/dl, p=0.006).

Protocol 2 was a dose-ranging study in 742 diet and exercise failed patients who were randomised to receive metformin SR 500 mg, 1000 mg, 1500 mg or 2000 mg once daily or 1000 mg twice daily or placebo for 16 weeks. After 16 weeks, the treatment differences in HbA_{1C} versus placebo were -0.6% with 500 mg daily, -0.7% with 1000 mg daily, -1.0% with 1500 mg daily, -1.0% with 2000 mg daily and -1.2% with 1000mg twice daily. At week 16, the proportion of patients achieving HbA_{1C} <7% was 34% and 36% in metformin SR 1500mg once daily and 2000mg once daily groups respectively compared to 10% in the placebo group. As in the previous protocol, changes in fasting blood glucose were similar to the effects on HbA_{1C}. At week 16, there were significant reductions in LDL-cholesterol with all doses of once daily metformin SR compared with placebo: mean changes versus placebo of -8.0mg/dl with 500mg, -7.0mg/dl with 1000mg, -11mg/dl with 1500mg and –10mg/dl with

2000mg ($p<0.05$-0.001). There was also a significant reduction in total cholesterol with the 2000mg metformin SR versus placebo (-8mg/dl, $p<0.05$). There was an increase in triglyceride levels in each of the metformin SR groups compared to placebo. This reached statistical significance in the metformin SR 1500mg daily group: mean change versus placebo 40mg/dl ($p<0.01$). The larger increase in this group was reported to be due to a significant number of outliers.

Summary of evidence on comparative safety

The most common adverse event with metformin is gastrointestinal disturbance, manifest as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These occur frequently during initiation of therapy and resolves spontaneously in most cases. Both the original submission and this resubmission contain details of a retrospective multi-centre, case-control trial of 468 type 2 diabetic patients (metformin IR (n=158) and SR (n=310)). The primary outcomes of the study were gastrointestinal tolerability and frequency of diarrhoea caused by metformin in both cohorts during the first year of treatment. There was no statistically significant difference in adverse events between the two groups (11.4% versus 11.9% respectively). The relative risk of any gastrointestinal adverse event for metformin SR compared to IR was 1.05 (95% CI: 0.62, 1.78; p=0.86). In the subgroup of patients (n=205) who switched from metformin IR to prolonged release there was a significant reduction in the percentage of patients reporting gastrointestinal adverse events in the year after switching compared to the year before switching (12% versus 26%, p=0.0006 for any gastrointestinal event and 8% versus 18% for diarrhoea, p=0.008). A further subgroup analysis, new to the resubmission, of those patients who had switched from IR to SR formulations with the aim of relieving gastrointestinal symptoms (n=78), showed that the incidence of any gastrointestinal adverse event and of diarrhoea were significantly reduced ($p<0.0001$ and p=0.0014, respectively). It should be noted that the study was not powered to detect significant differences in the subgroup analysis.

No new safety concerns were raised with metformin SR that were not known for metformin IR other than the uncertainty around the observed increases in triglyceride levels.

Other data were also assessed but remain commercially confidential.

Summary of clinical effectiveness issues

Metformin SR has shown equivalent glycaemic control, as measured by HbA_{1C}, to metformin in the short-term. However, the significant increase in triglycerides noted with the SR but not the IR formulation warrants further assessment. The evidence to show that this preparation is better tolerated than metformin is provided mainly by a retrospective, case control trial in 468 patients, which found no significant difference in its primary endpoint.

Summary of comparative health economic evidence

The economic evaluation compares metformin SR to sulphonylurea and rosiglitazone in adults with type 2 diabetes who are overweight and unable to tolerate metformin IR due to side-effects.

Patients enter the model as intolerant to metformin IR and receive metformin SR or sulphonylureas or rosiglitazone. During each six-month period, patients switch to different hypoglycaemic medication due to either adverse events (AEs) or poor glycaemic control. If

switch is due to loss of control, patients switch to another hypoglycaemic agent in addition to the therapy to which they had inadequate response. If switching is due to intolerance, patients change initially to sulphonylureas then rosiglitazone. There are a total of five lines with the final line being metformin SR plus insulin or sulphonylurea plus insulin or insulin only. Patients starting on a comparator never switch to metformin SR.

Clinical data come from trials augmented by a considerable number of assumptions that are explicit. Drug doses were estimated by a Scottish clinician and unit costs from the BNF. Cost of diabetic events avoided were derived from patient level data in the UKPDS study.

The results show that metformin SR dominates the comparators. It is the cheapest, (saving some £0.5m in drug costs and £1.4m in avoided adverse clinical events compared to sulphonylureas) and yields the greatest gain in life years. Extensive sensitivity analyses show the results are robust to wide changes in parameter values.

This is a well presented economic evaluation using data from trials, setting out explicit assumptions where these are used and adopting extensive sensitivity analyses recognizing the uncertainty. The main weaknesses are:

1. There is no utility analysis
2. Key data e.g. adverse events during subsequent 6 months for metformin SR, are not available.
3. The key assumption is that efficacy of metformin SR is equivalent to metformin IR in patients intolerant to metformin IR but the clinical evidence base for this is not convincing.

Patient and public involvement

Patient Interest Group Submission: Diabetes UK Scotland

Budget impact

The budget impact assumes that 2,400 patients in Scotland cease treatment with metformin IR each year, with between 25% and 75% being suitable to receive metformin SR.

If 69% and 31% of such patients would use sulphonylurea and rosiglitazone respectively, then there would be direct savings of around £120 per patient per year from introducing metformin SR (assumes metformin SR costs around £80 per year).

The annual savings range from an estimated £52,000 in year 1 to £85,500 in year 5 assuming 25% switch to metformin SR; the equivalent figures assuming 75% switching are £155,400 and £256,400.

Guidelines and protocols

Scottish Intercollegiate Guidelines Network. Management of Diabetes. SIGN Publication No. 55. November 2001

National Institute for Health and Clinical Excellence (NICE). National Clinical Guidelines for Type 2 Diabetes. Management of blood glucose. September 2002.

Additional information

SMC issued the following advice on the original submission for this product in December 2004:

"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."

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 11 November 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* http://www.scottishmedicines.org.uk/

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Fujioka K, Pans M and 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.

Fujioka K, Brazg RL, Raz I et al. Efficacy, dose response relationship and safety of a once-daily extended-release metformin (Glucophage XR) in type 2 diabetic patients with inadequate glycaemic control despite prior treatment with diet and exercise: results from two double-blind, placebo-controlled studies. Diabetes, Obesity and Metabolism, 2005; 7:28 – 39.

Blonde L, Dailey GE, Jabbour SA et al. 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.

Davidson J, Howlett H. New prolonged-release metformin improves gastrointestinal tolerability. Br J Diabetes Vasc Dis 2004; 4: 273-7.