National Essential Medicine List
Primary Healthcare Medication Review Process
Component: Endocrine medicines

Medication name: Glimepiride

Date of review: January 2014

Indication: Treatment of diabetes mellitus type 2 in the elderly and in patients with mild renal impairment.

Executive summary:

Compared with gliclazide, glimepiride has similar efficacy, but might be associated with increased mortality risk.

Introduction and contextualisation:

The current primary and adult hospital level EMLs and STGs for diabetes mellitus type 2 include the sulphonylureas gliclazide and glibenclamide for patients who are not controlled on diet, exercise and metformin. Two external reviewers requested that glimepiride be added. One suggested that it should replace glibenclamide as it is associated with a lower risk of hypoglycaemia and cardiovascular events, and it may be given as a single daily dose which might improve adherence. A committee member suggested that the committee investigate whether glimepiride could replace gliclazide instead.

This review explores the efficacy and safety of glimepiride compared to gliclazide.

Search strategy:

Pubmed search terms:

Randomised controlled trials

("glimepiride"[Supplementary Concept] OR "glimepiride"[All Fields]) AND ("gliclazide"[MeSH Terms] OR "gliclazide"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomised controlled trial"[All Fields] OR "randomized controlled trial"[All Fields])

Observational studies

("glimepiride"[Supplementary Concept] OR "glimepiride"[All Fields]) AND ("gliclazide"[MeSH Terms] OR "gliclazide"[All Fields])

Selection of studies:

Inclusion criteria:

Types of studies: randomised controlled trials (RCTs) or prospective or retrospective observational cohort studies
Participants: patients with diabetes mellitus type 2
Interventions: glimepiride

Control: gliclazide
Outcomes: Efficacy: glucose concentrations and HbA1c
Safety: risk of hypoglycaemia and cardiovascular effects
Mortality

Results:
Randomised controlled trials

The Pubmed search identified 7 studies. Four met the inclusion criteria. A further (potentially eligible) study was identified in the broader (second) search.

Observational studies
The PubMed search identified 102 studies. Six met the inclusion criteria.

Evidence synthesis:

Randomised controlled trials

Efficacy and risk of hypoglycaemia

Gliclazide
A trial in 230 type 2 diabetics who were uncontrolled on diet or glibenclamide were allocated to receive 1–6 mg glimepiride daily or 40–160 mg gliclazide daily for 24 weeks.[1] (The authors do not state whether or not the treatment allocation was randomised.) There were no significant between-group differences in changes in fasting blood glucose, HbA1c or incidence of hypoglycaemia.

A RCT in 172 uncontrolled type 2 diabetics randomised patients to continue their current sulphonylurea (gliclazide or glibenclamide) or to switch to glimepiride.[2] There were no significant changes from baseline in HbA1c after six months' treatment in either group.

Modified release (MR) gliclazide
A RCT in 60 newly diagnosed type 2 diabetics randomised patients to repaglinide, glimepiride or gliclazide MR for one month (starting doses of 3mg, 1 mg and 30 mg daily respectively, titrated to effect). There were no significant between-group differences in changes in fasting blood glucose, HbA1c or incidence of hypoglycaemia.[3]

A RCT in 845 type 2 diabetics randomized patients to 1–6 mg glimepiride daily or 30–120 mg gliclazide MR daily for 27 weeks. Reductions in HbA1c were similar, but the incidence of hypoglycaemia was significantly higher in the glimepiride group: 8.9 versus 3.7%, odds ratio 2.5 (95% confidence interval 1.4 to 4.7).[4]

Vascular effects

A crossover RCT in 12 type 2 diabetic patients compared glimepiride and gliclazide over four weeks. There were no significant differences in arterial stiffness, pressor responsiveness, or vasodilator function.[5]

Observational studies

Mortality
A retrospective cohort study in 107 806 patients in Denmark found that glimepiride monotherapy significantly increased the risk of mortality compared to metformin, but gliclazide did not: odds ratio (95% confidence interval) 1.32 (1.24 to 1.40) and 1.05 (0.94 to 1.16) respectively.[6]

A retrospective cohort study in 3 477 patients with heart failure in Denmark found no difference in mortality between glimepiride, glibenclamide, glipizide, gliclazide or tolbutamide monotherapy.[7]

A retrospective cohort study in 9 876 type 2 diabetics who had a myocardial infarction and who were not treated by percutaneous coronary intervention found that glibenclamide, glimepiride, glipizide and tolbutamide, but not gliclazide, were associated with an increased risk of cardiovascular mortality or non-fatal myocardial infarction compared to metformin. Hazard ratios (95% confidence intervals: 1.31 (1.17 to 1.46); 1.19 (1.06 to 1.32); 1.25 (1.11 to 1.42); 1.18 (1.03 to 1.34); and 1.03 (0.88 to 1.22) respectively.[8]

A prospective cohort study in 1 310 patients in France found no significant difference in in-hospital mortality after a myocardial infarction between glimepiride and gliclazide (1.5 versus 1.8% respectively, p=0.33).[9]

A retrospective cohort study in 64 266 patients in the Ukraine found that all-cause mortality was higher in those on glimepiride than those on gliclazide: hazard ratio 1.846 (95% confidence interval 1.192 to 2.898).[10]

A retrospective cohort study in 2 002 patients in Italy reported annual mortality rates of 0.4% for patients on glimepiride plus metformin; 2.1% for patients on gliclazide plus metformin; and 8.7% for glibenclamide plus metformin.[11]

Evidence quality:
This review considers both randomised controlled trials and observational cohort studies. While there are many limitations to the observational studies, they are presented to give an indication of mortality as the RCTs did not have large enough samples or duration of follow up to estimate that.

Alternative agents:
The EML and STG currently list glibenclamide and gliclazide.

Summary:
Several small randomised controlled trials demonstrated that glimepiride and gliclazide have similar efficacy. Three observational studies directly compared gliclazide and glimepiride: two found no difference in mortality, but one found that mortality was significantly higher with glimepiride. One study reported annual mortality rates but didn't directly compare gliclazide and glimepiride. Two studies didn't directly compare gliclazide and glimepiride, but found that

glimepiride was associated with increased mortality risk relative to metformin, but gliclazide was not.

Recommendations:

- Consider glimepiride and gliclazide to be equivalent for diabetes mellitus type 2.
- Glimepiride is preferred in the elderly and in patients with mild renal impairment.
- Glibenclamide be retained in the PHC EML as a long acting sulphonylurea.

Rationale:

- *Efficacy and safety:*
  - Gliclazide is considered equivalent to glimepiride, in terms of efficacy. Effect size of mortality benefit in observational studies was small and inconsistent across the studies, not considered clinically relevant.
- *Half lives:*
  Gliclazide was considered to have a half life comparable to that of glibenclamide.
  - It was reported that the half lives for sulphonylureas were:
    - Gliclazide = 10-12 hours
    - Glibenclamide = 10 hours
    - Glimepiride = 5-8 hours
  - Glimepiride is the shortest acting sulphonylurea (compared to glibenclamide and gliclazide).

Level of evidence: II RCTs

References:

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