Expert peer review on application for the inclusion of gliclazide, glipizide or glimepiride as alternatives to glibenclamide

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes ✓  No  (if no, please provide reference and information)

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

      Based on surrogate outcomes (notably changes in plasma glucose or HbA1c), there are no significant differences in the efficacy of glibenclamide, gliclazide, glipizide or glimepiride in the treatment of type 2 diabetes mellitus.

   c. Please provide any additional relevant information with reference

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes ✓  No  (if no, please provide reference and information)

   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

      Although comparators have varied, depending on the setting, data from observational studies (retrospective cohort studies and chart reviews) as well as a meta-analysis of randomised controlled trials, have indicated that there is an increased risk of hypoglycaemia associated with the use of glibenclamide, as opposed to other sulphonylureas, and that this risk is elevated in the elderly.

   c. Please provide any additional relevant information with reference

3. Assessment of cost and availability
   a. Have all relevant data on cost and availability provided
      Yes ✓  No  (if no, please provide reference and information)

   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

      Based on MSH International Drug Price Indicator data, the median procurement prices for glibenclamide ($0.852 for a questionably high maximum of 20mg/day) are somewhat lower than those for gliclazide ($2.832 for 320mg/day). Cost comparisons using US data are complicated by the lack of gliclazide on that market, and there
are no MSH data for glipizide and glimepiride. However, the relative prices of glibenclamide and gliclazide may reflect existing sales volumes in the countries that are included in the MSH survey. It is clear from available country EMLs that there is widespread access to gliclazide (included on 50% of 40 lists), even though glibenclamide still dominates (97.5% of 40 lists).

c. Please provide any additional relevant information with reference

d. Is the product available in several low and middle income countries?

While gliclazide is not registered in the US, it appears to be widely available in a range of countries, as shown by its inclusion in country EMLs. Access to glipizide and glimepiride is more limited, at least by this measure.

4. Assessment of public health need

a. Please provide the public health need for this product (1-2 sentences)

The need for an effective, safe and affordable oral hypoglycaemic agent is clearly demonstrated. Diabetes mellitus is common in all countries and is particularly prevalent in the elderly.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

Although the most recent WHO guidance (Prevention and control of NCDs: Guidelines for primary health care in low-resource settings, Oct 2012 – accessible at http://apps.who.int/iris/bitstream/10665/76173/1/9789241548397_eng.pdf) makes mention of glibenclamide being the only sulphonylurea listed on the WHO Model EML, it does also provide some data on glipizide, gliquidone, gliclazide and glimepiride (in terms of dosea and durations of action). It notes that glibenclamide is “most likely to be available in low-resource settings”, but add this cautionary note: “As precaution against severe hypoglycaemia, glibenclamide should be started with a small dose of 2.5-5 mg once daily with breakfast, and adjusted according to response to a maximum of 15 mg daily”.

5. Are there special requirements for use or training needed for safe/effective use?

If yes, please provide details in 1-2 sentences

No.

6. Is the proposed product registered by a stringent regulatory authority?

Yes ✓ No

7. Any other comments

Gliclazide is not registered by the US FDA.

8. What is your recommendation to the committee (please provide the rationale)

The proposal before the Committee is to retain glibenclamide, but to add gliclazide (with a square box symbol), specifically for the elderly (over 60 years), with a note to state that other agents other than glibenclamide are suitable options). Given the possibility of large differences in the relative prices of the competing sulphonylureas
at country level (as evidenced by the contrast between the MSH prices and those in the US), the potential for marked shifts in prices as sales volumes change, and the evidence of widespread access to gliclazide (which is no less effective than glibenclamide, but measurably safer in terms of its potential to cause hypoglycaemia), it is recommended instead that glibenclamide 2.5 and 5.0mg be replaced by gliclazide 80mg oral solid dosage form, with a square box symbol, and a note to the effect that glibenclamide is acceptable only when used in those under the age of 60 years. This would send the clear signal that glibenclamide is no longer a suitable stand-alone option.