Reviewer No. 1 checklist for:

Review of the use of oral antidiabetics in children

In order to decide about the inclusion of these medicines in the WHO Model Essential Medicines List

(1) Have all important studies that you are aware of been included?
   Yes X No 

(2) Is there adequate evidence of efficacy for the proposed use?
   Yes No X

(3) Is there evidence of efficacy in diverse settings and/or populations?
   Yes No X

(4) Are there adverse effects of concern?
   Yes No X

(5) Are there special requirements or training needed for safe/effective use?
   Yes No X

(6) Is this product needed to meet the majority health needs of the population?
   Yes No X

(7) Is the proposed dosage form registered by a stringent regulatory authority?
   Yes X No 

(8) What action do you propose for the Committee to take?
   I agree with Mr. Sackeyfio’s conclusion. There is not reliable evidence on the efficacy and safety of oral antidiabetic medicines in children. The identified evidence did not adequately address the question of which oral antidiabetic agent should be used in children under 12 years old. I also propose the discussion about the retaining of metformin in the List.

(9) Additional comment, if any.

Older studies refer the occurrence of type 1 diabetes in children and adolescents. Since this disease type was known as a consequence of absolute deficiency of pancreatic insulin, children were usually treated by exogenous insulin replacement. Nowadays, many children and adolescents are obese or overweight, being at risk of developing type 2 diabetes, which is normally associated with insulin resistance and obesity. This is the reason for having this discussion.
**Oral antidiabetic** medicines are commonly used for type 2 diabetes treatment in adults. Although these patients might be controlled only on diet and increasing physical activity, many also require an oral antidiabetic medicine or insulin (or both) to maintain satisfactory control. Two or three oral antidiabetics have accepted use for patients (especially if overweight) whose glycaemic control is inadequate despite the use of one or two oral antidiabetics and for who are unable or unwilling to take insulin.¹

Oral antidiabetic agents can also be used as insulin sensitizers in type 1 diabetes. The current oral antidiabetic medicines are: **sulfonylureas** (glibenclamide, glimepiride, glicazide), **biguanides** (metformin), **thiazolidinediones** (pioglitazone, rosiglitazone), **intestinal alpha-glucosidase inhibitors** (acarbose), **dipeptidylpeptidase-4 inhibitors** (sitagliptin, vildagliptin, saxagliptin), and **meglitinides** (repaglinide, nateglinide).

Pramlintide (synthetic amylin analog), exenatide and liraglutide (incretins) are given by subcutaneous injection for the treatment of type 2 diabetes mellitus.

Sulfonylureas are considered the first choice in non-obese adults with type 2 diabetes. Metformin is the preferential oral antidiabetic in obese or overweight adults with type 2 diabetes. The other antidiabetic agents are accepted for restricted use for the treatment of type 2 diabetes in adults, in combination with metformin or sulphonylurea (or both) or as an alternative to treatment with insulin in patients in which treatment with metformin or sulphonylurea (or both) at maximally tolerated doses has been inadequate.¹

In the updated second WHO Model List of Essential Medicines for Children (March 2010) only metformin (500mg tablet) is included in the complementary list.

**EVIDENCE OF ORAL ANTIDIABETIC MEDICINES EFFICACY IN CHILDREN**

Even in adults, the known evidence of efficacy is limited, due to studies with methodological problems. The measurement of efficacy is done through surrogate (hospitalization, for example) or intermediate endpoints, as biochemical ones (plasma fasting glucose, total glycosylated or glycated haemoglobin [HbA₁] or a specific fraction [HbA₁c], plasma fasting insulin, lipid profile), instead of hard outcomes, such as symptomatic improvement, quality of life, risk of co-morbidity, and mortality.

In children, the role of oral antidiabetic agents in type 2 diabetes control has scarce evidence. Stronger evidence from high-quality studies of longer duration and larger sample size are required before clinical conclusions about the optimal treatment protocol in this population can be drawn.

In children, some of the relevant chronic outcomes are unable to be apparent, due to insufficient time for developing. There are not useful findings for applying to children under the age of 5.

Reviewing this issue in children, I did not find different studies from those mentioned in the previous review. However, there is current research about metformin effects in adolescent obesity and insulin resistance.
SULFONYLUREAS
There is limited experience with the use of sulfonylureas in children. In a multicentre study (n= 285 participants; mean age of 13.8 years), children with type 2 diabetes were randomized to receive glimepiride or metformin for 26 weeks. Both oral anti diabetic medicines showed similar biochemical endpoints, or hypoglycaemia incidence. Glimepiride presented greater weight gain, in comparison to metformin.  

In conclusion, sulfonylureas present the disadvantage of weight gain, which allows its use only for lean patients.

BIGUANIDES
In 2005, Kane et al. reported metformin as the only antidiabetic approved for use in pediatrics. Although the authors concluded that metformin is effective, they also commented that monotherapy in this population would unlikely to be enough for sustained effects.

A systematic review (4 randomized clinical trials placebo-controlled) and meta-analysis of three of these studies evidenced that metformin improved markers of insulin sensitivity and reduced body mass index (BMI) in children and adolescents with clinical insulin resistance or pre-diabetes. Mild gastrointestinal symptoms were reported in 19% (2%-29%) of participants taking metformin.

A new Cochrane review of two RCTs (60 participants; 14 to 20 years old) investigated the effect of metformin added to insulin therapy in type 1 diabetic adolescents. Meta-analysis was not possible due to the clinical and methodological heterogeneity of data. The results showed improvement of metabolic control with the combined therapy. No data on health-related quality of life, all-cause mortality or morbidity was currently available. Adverse effects were mainly gastrointestinal in both studies and hypoglycaemia in one study. Stronger evidence is required from larger studies, carried out over longer time periods to document long-term effects in relevant clinical outcomes.

The table bellow intends to show the advantages and disadvantages of metformin in order to decide about its remaining in the List for diabetic children.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>Approved use in children</td>
<td>Scarce evidence of benefit</td>
</tr>
<tr>
<td>Improved insulin sensitivity</td>
<td>No evaluation of hard endpoints</td>
</tr>
<tr>
<td>Reduced body mass index (BMI) in obese diabetic patients</td>
<td>Variability in results about BMI reduction</td>
</tr>
<tr>
<td>Mild gastrointestinal symptoms</td>
<td>Need to be added to diet and exercise program or insulin or other oral antidiabetics</td>
</tr>
<tr>
<td>Efficacy as insulin sensitizer in type 1 diabetes</td>
<td>Absence of studies conducted in children under 12 years old</td>
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<td>Affordable cost</td>
<td></td>
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</tbody>
</table>
Metformin has also been studied focusing obesity in children and adolescents without diabetes.
A systematic review and meta-analysis of five randomized, double-blind, placebo-controlled trials (n = 320 participants; ≥19 years), performed in obese subjects without diabetes showed moderate reduction in BMI and insulin resistance during 6 months of evaluation. Larger, longer-term studies in different populations are needed to establish its role in the treatment of overweight children.6

A multicenter, randomized, double-blind, placebo-controlled trial enrolled 78 obese adolescents (aged 13-18 years) for receiving metformin hydrochloride XR (2000 mg, once daily) or an identical placebo, added to a lifestyle intervention program for 48 weeks. Metformin reduced BMI in comparison to placebo (P = 0.03). This difference persisted for 12 to 24 weeks after cessation of treatment. 7

About this trial, Park and Sanjay8 commented the need of larger sample sizes. Besides, they observed that only a small proportion of participants were available at final follow-up, raising the possibility of a bias in results.

Another study randomized obese adolescents (n=70; mean age =13.8 years) with previous 6 month-unsuccessful lifestyle intervention to receive metformin (2×500 mg/day; n=36) or placebo (n=34) in addition to ongoing lifestyle intervention for another 6 months. Insulin sensitivity markers improved similarly in the placebo and metformin groups (P=0.048), but BMI remained unchanged. Most differences did not reach statistical significance, probably due to improved compliance with lifestyle intervention as a placebo effect. In addition, the metformin dose may be too low.9

So, the results, once again, are not impressive, perhaps for methodological problems.

In conclusion, it has to be balanced the probable benefits of metformin against the lack of evidence of its efficacy and safety in children who do not improve his diabetic disease with non-pharmacologic strategies. Additionally, there is evidence that educational programmes for parents/caregivers, focusing on diet, physical activity and glucose regular monitoring, can have positive role in children diabetes.

The modest benefit in obese or overweight non-diabetic adolescents does not seem to me a real reason for metformin retaining in the list.

OTHER ORAL ANTIDIABETICS
A small randomized, double-blind, placebo-controlled crossover trial10 evaluated rosiglitazone (4 mg, twice daily, for 24 weeks) as an insulin sensitizer, on glycaemic control and insulin resistance in 28 normal weight adolescents (age 10-18 years) with type 1 diabetes mellitus, maintained on the same insulin regime. Compared with placebo, rosiglitazone resulted in decreased insulin dose, but no significant change was observed in insulin sensitivity. No adverse events were attributable to rosiglitazone.

A randomized, double-blind, placebo-controlled trial (n=60 type 1 diabetic lean adolescents)11 analyzed the effect of pioglitazone (30mg, once daily, for 6 months) as an adjunctive therapy in patients in insulin therapy. Pioglitazone was modestly effective adjunct to insulin therapy in lean type 1 diabetic subjects. It improved post-
prandial glucose levels and HbA1c, without alterations in body weight and insulin requirement. Minor hypoglycaemic episodes occurred in both pioglitazone and placebo groups. No major hypoglycaemic events were observed. 

**Acarbose** is avoided in pregnancy and in breast-feeding. The medicine is recommended for adult over 18 years old. ¹

No evidence was identified for the use of **dipeptidylpeptidase-4 inhibitors** in children.

No evidence was identified for the use of **metiglinides** in children.

**In conclusion, I do not see a reliable reason to include these oral antidiabetic agents in the Model List for children.**

References: