HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 March 2006

GLUCOPHAGE 500 mg, film-coated tablet
Box of 30 tablets - CIP code: 352 816-7

GLUCOPHAGE 850 mg, film-coated tablet
Box of 30 tablets - CIP code: 304 480-2

GLUCOPHAGE 1000 mg, film-coated tablet
Box of 30 tablets - CIP code: 356 017-1

Merck Sante SAS

metformin (hydrochloride)

List I

Date of Marketing Authorisations:
First granted visa for a medicinal product based on metformin: 19 March 1959. Il faut que cela reste homogène d'un avis à l'autre
Glucophage 500 mg, box of 30 tablets:10 December 1999,
Glucophage 850 mg, box of 30 tablets: 29 November 1967,
Glucophage 1000 mg, box of 30 tablets:10 January 2001,
amended on 25 October, 2004 (extension of indication in children aged over 10 years)

Reason for application:
Inclusion on the list of products reimbursed by National Insurance and approved for use in hospitals in the indication of children with type 2 diabetes aged over 10 years.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

metformin (hydrochloride)

1.2. Background

First oral antidiabetic with an indication in children aged over 10 years.

1.3. Indications

Treatment of type 2 diabetes, particularly in patients who are overweight, when dietary management and physical exercise do not result in adequate glycaemic control.

- In adults, Glucophage may be used as monotherapy or in combination with other oral antidiabetics or with insulin.
- ***In children aged over 10 years and in adolescents, Glucophage may be used as monotherapy or in combination with insulin***.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adults treated with metformin as first-line therapy, after failure of dietary measures.

1.4. Dosage

see SPC.

Children and adolescents

As monotherapy or in combination with insulin:

- GLUCOPHAGE 500 mg, film-coated tablet, may be used in children aged over 10 years and in adolescents.
- The usual starting dose is one 500 mg or 850 mg tablet once a day, taken during or after meals.
- After 10–15 days, the dose may be adjusted according to blood glucose concentration. A gradual increase in dose may improve the gastrointestinal tolerance. The maximum recommended dose of metformin is 2 g a day, taken in 2 or 3 doses

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

A : Alimentary tract and metabolism
A10 : Drugs used in diabetes
A10B : Blood glucose lowering drugs excl insulins
A10BA: Biguanides
A10BA02 : Metformin

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

There are no other oral antidiabetic with an indication in children

2.3. Medicines with a similar therapeutic aim

Insulin.

3 ANALYSIS OF AVAILABLE DATA IN CHILDREN

In children, the company has submitted the results of a double-blind trial with an open extension.

3.1. Trial CV 138-09 (Jones et al. Diabetes Care 2002,25)

This was a randomised, double-blind trial, conducted in type 2 diabetic patients aged 10–16 years, comparing metformin with placebo, after 16 weeks of treatment.

The main endpoint was the change in fasting plasma glucose (FG) between the start of treatment and week 16. Secondary endpoints were HbA1c, weight, body mass index (BMI), lipid profile and C-peptide value.

The initial dose was 500 mg of metformin, twice a day. This could be increased up to 2 g a day.

Results: it should be noted that glycaemic balance ? differed between the groups at inclusion.

	placebo	Metformin
Number of patients randomised	40	42
Baseline FG (g/L)	1.98 ± 0.60	1.66 ± 0.50
Change in FG between start and end of treatment (g/L)	+ 0.21	- 0.43*
Baseline HbA1c (%)	8.9	8.2
HbA1c at end of treatment (%)	8.6	7.5*

*p<0.001 vs placebo

There was a significant difference in favour of metformin regarding change in fasting glycaemia between baseline OK and end of treatment, and in regard to HbA1c at end of treatment. There was no significant difference between the 2 treatment groups for the other criteria.

The adverse events reported were of the same type as those normally seen in adults. Abdominal pain (9 versus 5) and nausea/vomiting (5 versus 0) were more common under metformin than under placebo.

3.2. Trial CV 138-09 – open extension

The patients included in the above trial could continue treatment with metformin in an open study, being treated either with metformin alone, or with a combination of metformin + insulin, up to 52 weeks.
Sixty-seven patients were included in this study, 14 of whom were treated with the combination insulin + metformin.
Although conducted in a small number of patients, this study confirmed the safety profile of metformin in children, as observed in the previous trial.

3.3. Conclusion

The assessment of the efficacy and safety of metformin in children is based on a double-blind randomised clinical trial carried out in a small number of type 2 diabetic patients aged 10–16 years, comparing metformin versus placebo, after only 16 weeks of treatment.
There was a significant difference in favour of metformin regarding change in fasting glycaemia between baseline and end of treatment, and with regard to HbA1c at end of treatment. The relevance of this difference is difficult to interpret because glycaemic balance at inclusion was different in both groups.
The adverse events experienced je préfère reported were consistent with those normally observed in adults.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Type 2 diabetes is a chronic disease with potentially serious complications.
GLUCOPHAGE is a treatment for hyperglycaemia.
Current data suggest that the efficacy/undesirable effects ratio for these drugs is high.
There is only one medicinal alternative to this drug in children, i.e. insulin.
These drugs are first-line medicines.

Public Health Benefit:

Type 2 diabetes is a significant public health burden. As the subpopulation concerned by the indication (type 2 diabetic children older than 10 years and adolescents in whom diet and physical exercise are not sufficient) is small, it represents a minor public health burden.

Improving the management of type 2 diabetes in children is a public health requirement.
The availability of an oral antidiabetic should partially satisfy this requirement.

According to the available data, the impact on mortality and morbidity that Glucophage could provide (compared with insulin therapy) cannot be quantified.

Nevertheless, insofar as this treatment partially satisfies a public health requirement, it is anticipated that this medicinal product would be of benefit to public health in this indication. This benefit is minor.

The actual benefit of Glucophage is substantial in children, although type 2 diabetes is very uncommon, as reflected in the small number of children included in the trial.

4.2. Improvement in actual benefit

Despite the methodological weakness of the trial presented by the company, and in view of the therapeutic need not covered in the age range concerned, Glucophage contributes a moderate improvement in actual Benefit (level III IAB) compared with the usual strategy for managing type 2 diabetes in children aged over 10 years and adolescents.

4.3. Therapeutic use

Dietary measures and physical activity are the initial treatment for type 2 diabetes. They should be started as soon as the diagnosis is confirmed, and continued indefinitely.
Oral antidiabetics are prescribed after lifestyle and dietary measures have failed.

In children aged over 10 years, metformin is the only oral antidiabetic indicated. However, type 2 diabetes is very rare in this population. Insulin may also be prescribed and was the only treatment available until now.

4.4. Target population in children

The onset of type 2 diabetes in children coincides with the epidemic of obesity in industrialised countries. There is no French registry for diabetes in children, but of the 370 cases of diabetes diagnosed in a single Paris paediatric centre between 1993 and 1998, 8 were classified as type 2 diabetes (*Journées de diabétologie 2003* – Anne Fagot-Campagna).

According to CNAMTS[1] in January 2005, there were 303 applications for reimbursement of an oral antidiabetic alone (n=267) or an oral antidiabetic combined with insulin (n=36) for children aged 10–17 years.
Considering that the general reimbursement scheme represents 72% of applications for reimbursement, the target population for Glucophage would be in the order of 350–500 children aged 10–17 years.

4.5. Transparency Committee recommendations

The Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in a paediatric indication.

The Transparency Committee would like a study to be carried out among children and adolescents treated with Glucophage for diabetes. The aim of this study would be to determine under normal treatment conditions:

- the conditions under which this medicinal product is used (profile of patients treated including age, BMI, type of diabetes and compliance with the Marketing Authorisation, previous treatment including in particular diet, physical exercise, insulin therapy, etc),
- change in HbA1c level under treatment,
- how often patients move on to insulin therapy and the mean period of occurence.

The study duration should be determined by a scientific committee; reasons should be given for the duration chosen, and it should be sufficient to satisfy the Committee's requirements.

4.5.1. Packaging: appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%

[1] National Health insurance fund for salaried workers