HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 July 2006

Xenical 120 mg, hard capsules
blister strips containing 84 capsules – CIP code: 347 809-6

Applicant : ROCHE

orlistat

list I

Date of initial Marketing Authorisation: 29 July 1998 – last amendment 31 May 2006

Reason for request: inclusion on the list of drugs reimbursed by National Insurance and approved for hospital use. The company is asking for listing only for obese patients under the age of 60 with metabolic syndrome defined according to NCEP ATP III criteria and with abnormal biochemistry values below the thresholds for drug therapy for each risk factor considered individually.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Orlistat

1.2. Indications

Xenical (orlistat) is indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients (body mass index (BMI) ≥30 kg/m2), or overweight patients (BMI ≥28 kg/m2) with associated risk factors.

Treatment with orlistat should be discontinued after 12 weeks if patients have been unable to lose at least 5% of their initial weight measured at the start of drug therapy.

1.3. Dosage

- Adults

The recommended dose of orlistat is one 120 mg capsule taken with water immediately before, during or up to one hour after each main meal. If a meal is missed or contains no fat, the dose of orlistat should be omitted.

The patient should be on a mildly hypocaloric, nutritionally balanced diet that contains approximately 30% of calories from fat. The diet should be rich in fruit and vegetables. The daily intake of fat, carbohydrate and protein should be spread over three main meals.

Data on doses above 120 mg three times daily have not shown any additional benefit.

The effect of orlistat results in an increase in faecal fat 24 to 48 hours after dosing. Upon discontinuation of therapy, faecal fat content usually returns to pre-treatment levels within 48 to 72 hours.

- Special populations

The effect of orlistat has not been studied in patients with hepatic and/or renal impairment, in children or in the elderly.

Orlistat should not be used in children.

1.4. Pharmacodynamic properties

Orlistat is a gastrointestinal lipase inhibitor.

2 REMINDER OF COMMITTEE OPINIONS AND LISTING CONDITIONS

Opinion of 10 May 2000

The actual benefit of Xenical for obese diabetics is insufficient to justify its reimbursement on the basis of the current dossier.

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2005)

A : ALIMENTARY TRACT AND METABOLISM
A08 : ANTIOBESITY PREPARATIONS, EXCLUDING DIET PRODUCTS
A08A : ANTIOBESITY PREPARATIONS, EXCLUDING DIET PRODUCTS
A08AB : PERIPHERALLY ACTING ANTIOBESITY PRODUCTS
A08AB01 : Orlistat

3.2. Medicinal products in the same therapeutic category

No other medicinal products are currently included on the list of products reimbursed by National Insurance in the treatment of obesity.

Sibutral (sibutramine) has a similar indication and is not reimbursed by National Health Insurance. It is indicated as auxiliary therapy in a weight control programme:

- in patients with nutritional obesity and body mass index (BMI) ≥30 kg/m^2
- in patients with nutrition-related overweight and BMI ≥27 kg/m^2 with concomitant risk factors related to obesity, such as type 2 diabetes or dyslipidaemia.

Sibutral may only be prescribed to patients who have not responded satisfactorily to an appropriate low-calorie diet, i.e. patients who have had difficulty in reaching or maintaining weight loss >5% in 3 months.

Sibutral should only be given as part of a global long-term obesity management programme, under the supervision of a doctor experienced in treating obesity.

3.3. Medicinal products with the same therapeutic aim

Not applicable

4 ANALYSIS OF AVAILABLE DATA

The company submitted results from:

- 5 studies in overweight patients with risk factors or obese patients, treated for 1–2 years (BMI between 28 and 43 kg/m^2)
- 7 studies in obese or overweight patients with diabetes inadequately controlled by treatment with oral antidiabetics and/or insulin (BMI between 28 and 43 kg/m^2).
- the XENDOS study to assess the long-term efficacy of Xenical on weight loss and prevention of onset of type 2 diabetes in obese patients (BMI ≥30 kg/m^2)
- a meta-analysis of 21 trials.

4.1. Efficacy

4.1.1. Studies in overweight patients (BMI >28) with risk factors or in obese patients

Five double-blind randomised trials comparing the effect of different doses of Xenical with placebo in patients treated for 1 or 2 years depending on the study. For the first year, treatment included a mildly hypcaloric diet. The primary endpoint was the change in weight between the start and end of treatment. The company pooled the results of the 5 studies and only listed results for patients treated with Xenical at the dose of 120 mg dose 3 times daily or with placebo (Table 1).

Table 1. Change in weight in the 5 pooled studies

	Orlistat 120 mg n=1561 kg	Placebo n=1119
Weight at inclusion (kg)	97.0	97.1
Weight loss after 1 year of treatment (kg)	-6.1	-2.6*

*p< 0.001

In the subgroup of patients who lost at least 5% of initial weight after 12 weeks of treatment, 49% (n= 765) of patients on Xenical and 40% (n= 448) on placebo responded[1]. There was no difference between the groups after 2 years of treatment, with a normal calorie diet for the second year.

4.1.2. Studies in obese or overweight type 2 diabetics treated with antidiabetic drugs

Seven randomised double-blind trials compared the effect of Xenical with placebo. Treatment also included a mildly hypocaloric diet. 2489 patients were randomised: 1255 to Xenical and 1234 to placebo. Treatment lasted between 6 months and 1 year depending on the study.

The primary endpoint was change in weight between the start and end of treatment and, depending on the study, change in HbA1c.

- *Results for weight:* in patients treated with Xenical, the mean difference in weight loss compared with placebo was 1.21 to 3.48 kg after 6 months and 1.83 to 3.3 kg in studies lasting 1 year. In all cases, weight reduction compared with placebo was statistically significant, although clinically small.

  After 1 year of treatment and pooling of all studies, 11.3% of patients had lost at least 10% of their weight on Xenical compared with 4.5% on placebo.

- *Results for HbA1c*: in 6 of the 7 studies, the reduction in HbA1c was statistically greater for Xenical than placebo (p< 0.05) after 6 months and 1 year of treatment. The mean reduction in HbA1c compared with placebo after 1 year of treatment was 0.18 to 0.55%. The effect on HbA1c was not shown to be independent of weight loss.

4.1.3. XENDOS trial

This was a randomised double-blind trial comparing Xenical 120 mg 3 times daily with placebo combined with a mildly hypocaloric diet in patients treated for up to 4 years. Primary endpoints were:

- time to onset of type 2 diabetes (blood glucose >2 g/L or 11.1 mmol/L, 2 h after oral glucose challenge),
- change in weight between the start and end of treatment.

A total of 3304 patients were randomised: 1649 to Xenical and 1655 to placebo. 52% (n=850) of patients on Xenical and 34% (n=564) of patients on placebo were treated for 4 years. Results are given in Table 2.

[1] Patients were responders if they had lost at least 10% of their initial weight after 1 year of treatment.

Table 2. Incidence of type 2 diabetes and weight loss in XENDOS trial

	Xenical	Placebo
Incidence of type 2 diabetes - N (%)	70 (6.15%)*	84 (9.04%)
Weight loss in the general population after 4 years of treatment (kg)	-5.8**	-3.0

*Hazard Ratio: 0.627 – p=0.0032 – Relative risk: -37.3%; **p<0.001

In the subgroup of patients who lost at least 5% of their initial weight after 12 weeks of treatment, 62% of patients on Xenical and 52% on placebo were responders after 1 year of treatment, and 21 percent of patients on Xenical compared with 10% on placebo were responders after 4 years of treatment[2].

A retrospective analysis was performed on 1320 obese patients with metabolic syndrome at inclusion (NCEP ATP III criteria) (Table 3).

Table 3. Change after 4 years of treatment in obese patients with metabolic syndrome

	Xenical N=672	Placebo N=648	p
Weight (kg)	-6.3.	-3.1	< 0.001
Waist circumference (cm)	-6.1	-3.7	< 0.001
Fasting blood glucose (mmol/L)	+0.1	+0.2	< 0.01
SBP (mmHg)	-5.5	-3.4	<.0.01
DBP (mmHg)	-3.3	-1.8	0.025
Incidence of type 2 diabetes	45 (9.8%)	54 (13.7%)	Hazard Ratio: 0.642 – p=0.03*

* Decrease in relative risk: -36.0%

4.1.4. Meta-analysis of 20 trials

A meta-analysis of the 20 randomised, double-blind, comparative trials with at least 6 months follow-up, and for which a database was available, was performed. Its aim was to assess the efficacy of Xenical on weight and/or on metabolic and cardiovascular risk factors.

These trials included 11 548 obese patients, 3399 of whom had metabolic syndrome[3] below the recommended thresholds for drug therapy. Of these, 559 patients had lost at least 5% of their weight after 3 months of treatment and were included in the analysis after treatment with Xenical for 12 months. 1573 patients were treated with placebo, 921 of whom were analysed after 12 months of treatment.

The percent change in weight from baseline and the relative change in the mean values for metabolic syndrome criteria after 1 year of treatment are given in Tables 4 and 5, respectively.

[2] Patients were responders if they had lost at least 10% of their initial weight.

[3] Definition of metabolic syndrome according to the NCEP/ATP III classification used by Roche:
Presence in one individual, of a combination of at least 3 of the following 5 criteria:
abdominal obesity with waist circumference (WC) >102 cm in men and > 88 cm in women
triglycerides ≥1.5 g/L (1.7 mmol/L)HDL-cholesterol < 0.40 g/L (1.04 mmol/L) in men and < 0.50 g/L (1.3 mmol/L) in women
fasting blood glucose > 1.10 g/L (6.1 mmol/L)
blood pressure ≥130/85 mmHg.

Table 4. Change in weight from baseline after 1 year of treatment

	Placebo N=921	Xenical N=559	Difference
Change (%)	-4.5	-11.4	-7.5 [-8.1;-6.8]*

*p=0.0001

Table 5. Relative change in mean values of metabolic syndrome criteria and LDL-C after 1 year of treatment

	Percent change [CI 95%]	
	Xenical (n=559)	Placebo (n=921)
Waist circumference	- 5.0 [- 5.7;- 4.4]	- 4.1 [- 4.6;- 3.5]
Triglycerides	- 8.3 [-12.3;- 4.4]	- 3.8 [- 6.8;- 0.9]
HDL-C	- 1.8 [- 3.6;+ 0.00]	+ 13.3 [+11.9; +14.7]
Fasting blood glucose	- 4.4 [- 5.28;- 2.19]	+ 3.7 [+2.5;+ 4.8]
SBP	- 3.4 [- 4.5;- 2.2]	- 1.6 [- 2.4;- 0.8]
DBP	- 4.6 [- 5.8;- 3.4]	- 2.1 [- 3,1;-1.3]
LDL-C	- 12.7 [- 14.7;- 10.8]	+ 6.3 [+ 4,0;+ 8.5]

The Transparency Committee had no statistical comparisons Xenical versus placebo at its disposal.

After 1 year of treatment, the prevalence of metabolic syndrome fell from 100% to 44% in patients treated with Xenical compared with 61% in patients on placebo.

4.2. Undesirable effects

The clinical development programme for Xenical involved 7027 patients and healthy volunteers. Of the patients, 2150 received orlistat for at least 1 year and 880 for 2 years. Nearly 30% of patients prematurely discontinued their treatment with Xenical 120 mg 3 times/day during the first year, usually because of adverse events.

Since Xenical was made available in 1997, 22 million patients worldwide have been treated.

Very common adverse events (>10%) have been: gastrointestinal disorders, mainly faecal (80% of patients on Xenical vs 57% on placebo), flu syndrome (40% of patients on Xenical vs 36% on placebo), headache (31% of patients on Xenical vs 28% on placebo) and, in obese type 2 diabetics, hypoglycaemia (13% on Xenical vs 10%).

Dermatological disorders have been reported: urticaria, rash, dermatitis, angioedema. A causal relationship with Xenical was suspected.

Rectal bleeding is now mentioned in the SPC.

4.3. Conclusion

The Transparency Committee regretted that it had no studies assessing the effect of Xenical on cardiovascular mortality and morbidity in the target population applied for by the company, i.e. obese patients under the age of 60 with metabolic syndrome defined according to NCEP ATP III criteria and with abnormal biochemistry values below the thresholds for drug therapy for each risk factor considered individually. In addition, some experts have questioned the definition of metabolic syndrome (Kahn et al, Diabetes Care 2005).

The only efficacy data concerned intermediate criteria.

In the 5 clinical trials in obese or overweight patients (BMI ≥28 kg/m²), Xenical combined with a mildly hypocaloric diet resulted in clinically significant weight loss compared with placebo (6.1 kg vs 2.6 kg) after 1 year of treatment.

In the 7 clinical trials in obese or overweight patients and type 2 diabetics, a mean of 11.3% of patients treated with orlistat for one year (120 mg, three times daily) lost at least 10% of their weight vs 4.5% of patients on placebo.

In 6 of the 7 studies, the reduction in HbA1c was statistically greater for Xenical than for placebo after 6 months and 1 year of treatment. However, the reduction was small (0.18 to 0.55%).

The aim of the XENDOS study was to assess the long-term efficacy of Xenical on weight loss and the prevention of onset of type 2 diabetes in obese patients (BMI $\geq$30 kg/m^2). There was a significant reduction in the incidence of type 2 diabetes (6% versus 9%), together with a significantly greater (but small) weight loss with Xenical than placebo, after a maximum of 4 years of treatment (5.8 kg vs 3.0 kg). A retrospective analysis including only obese patients with metabolic syndrome at inclusion showed a reduction in certain diagnostic criteria for metabolic syndrome with Xenical compared with placebo (waist circumference, fasting blood glucose, and blood pressure).

A meta-analysis of 20 comparative randomised double-blind trials with at least 6 months follow-up was carried out to assess the efficacy of Xenical on weight and/or metabolic and cardiovascular risk factors. After 1 year of treatment, weight loss (as percentage change from baseline) with Xenical was greater than with placebo. Mean values for metabolic syndrome criteria fell on Xenical treatment. There was no comparison with placebo. The prevalence of metabolic syndrome fell from 100% to 44% in patients treated with Xenical compared with 61% in patients on placebo.

The Committee did not have any data for assessing the consequences of discontinuing treatment on change in weight and metabolic criteria.

The most common adverse events were gastrointestinal.

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Obesity is a chronic disease with potentially serious consequences, in particular an increased risk of cardiovascular disease, hypertension, hyperlipidaemia and type 2 diabetes. Obesity-related risk of mortality and morbidity is related to excess weight.

Efficacy data for Xenical are based on intermediate criteria only. The efficacy/side effects ratio for Xenical is moderate.

There are no alternative drugs that are reimbursed.

Xenical is a second-line therapy, to be used if lifestyle and dietary measures followed for 3 months have failed.

Public health benefit:

Obesity is a substantial public health burden due to its morbidity, social impact, and detrimental effect on quality of life. As there is no consensus definition of metabolic syndrome, it is not possible to quantify the public health burden due to the subpopulation of patients with metabolic syndrome whose abnormal biochemistry values are below the thresholds of drug therapy for each of the risk factors in the syndrome.

Improving long-term management of obesity is a public health need. The response is not necessarily drug therapy.

The available data are insufficient to quantify the impact of Xenical on obesity-related morbidity and mortality associated with metabolic syndrome. According to the results of trials on weight and some cardiovascular risk factors, its expected theoretical impact in the short term is at most limited.
There is no guarantee that the results will translate into actual practice. A loss in effect is anticipated in clinical practice, in particular because:

- compliance is uncertain because of the digestive side effects of Xenical and the difficulty obese patients experience in complying with drug therapy combined with a hypocaloric diet;
- treatment-related weight loss is not maintained at a distance from Xenical discontinuation, if treatment is only given for a limited period;
- long-term safety data are lacking when Xenical is prescribed for an undefined and extended period;
- it is difficult to identify patients who might benefit from Xenical, particularly because of the problem of defining metabolic syndrome.

Consequently, no public health benefit is anticipated for Xenical.

The actual benefit of Xenical is insufficient in obese patients aged under 60 years with metabolic syndrome defined by NCEP ATP III criteria, whose abnormal biochemistry values are below the thresholds for drug therapy for each risk factor considered individually.

5.2. Improvement in actual benefit

Not applicable because AB is insufficient

5.3. Therapeutic use

Not applicable because AB is insufficient

5.4. Target population

Not applicable because AB is insufficient

5.5. Transparency Committee recommendations

The Committee did not recommend inclusion on the list of medicinal products reimbursed by National Health Insurance or on the list of medicinal products approved for use in hospitals and various public services in the indication proposed by the company, i.e. obese patients under the age of 60 with metabolic syndrome whose abnormal biochemistry values are below the threshold for drug therapy for each risk factor considered individually.