

Reduction of body weight and co-morbidities by orlistat: The XXL – Primary Health Care Trial

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Aim: The aim of this postmarketing surveillance (PMS) study was to investigate the effect of an orlistat therapy under the everyday conditions of our health care system.

Methods: 11 131 women and 4418 men from Germany [mean age 48 years, mean body mass index (BMI) 34.7 kg/m² and mean duration of obesity 13.7 years] were included. The patients were predominantly cared for by general practitioners. Four fifths of the patients reported having obesity-associated co-morbidities. All patients were advised to take orlistat 120 mg three times daily.

Results: After a mean treatment duration of 7.1 months, both women and men lost 10.7% of their baseline weight (87% lost > 5% weight and 51% lost > 10% weight). All cardiovascular risk factors improved markedly, and the intake of concomitant medications was either reduced or discontinued. Compared with baseline, 65% of the patients assessed their general state of health to have improved. For more than 90% of their patients, physicians described the success of the treatment as satisfactory, and most patients (62%) were willing to continue with the treatment.

Conclusions: The results obtained in this naturalistic PMS study were comparable with the results of randomised and placebo-controlled studies, which were performed predominantly in special care centres. Therefore, without any risk of adversely affecting the quality of treatment provided, the treatment of obese patients with orlistat may be transferred to general practitioners.

Keywords: anti-obesity agent, postmarketing surveillance study, weight loss, Xenical[®]

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Introduction

The increasing prevalence of obesity and its co-morbidities is a challenge for the health care system. In Germany, only one in three people have a body mass index (BMI) below the recommended level of 25 kg/m² [1]. However, within the past 20 years, the prevalence of overweight and obesity in children and adolescents has doubled [2]. To provide an effective treatment for this increasing population, it is necessary to involve both general practitioners, who would treat overweight and obese patients without any

co-morbidities, and physicians in special care centres, who should reserve the treatment they provide to those patients with co-morbidities or psycho-social problems.

The efficacy of orlistat, a gastrointestinal lipase inhibitor that reduces dietary fat absorption by approximately 30%, has been proven in many randomised and placebo-controlled trials. For example, the European Multicentre Study Group reported a weight reduction of 10.2% from baseline and an improvement of all cardiovascular risk factors after 2 years of treatment with

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orlistat and lifestyle changes [3]. Orlistat has also proved to be effective at weight reduction and glycaemic control in patients with diabetes, irrespective of whether they were receiving insulin therapy [4,5]. In the four-year XENical in the prevention of Diabetes in Obese Subjects trial (XENDOS), which studied 3304 patients, the relative risk of progression to type 2 diabetes was reduced by 37% with orlistat compared with placebo [6].

A weight reduction of 5% in obese patients is considered sufficient to obtain a noticeable improvement in morbidity and quality of life. For patients with a BMI of 35 kg/m², a weight reduction of more than 10% would be the target [7]. In the present study, the treatment of obese patients was transferred to general practitioners, who, in Germany, have the task of providing outpatient treatment. We assessed the effectiveness of orlistat treatment in combination with lifestyle changes in achieving these weight reduction targets in a large number of practices. The aim of the study was not to investigate the effect of orlistat on the different clinical parameters, but to examine the therapeutic outcome under everyday conditions of our health care system.

Methods

Patients

The postmarketing surveillance (PMS) study was performed between March 1999 and April 2000 in Germany, and following legal requirements, it was carried out in accordance with the requirements of the German national authority (BfArM). Physicians, who were routinely visited by field representatives of Hoffmann-La Roche AG, were asked to participate in this PMS study. As specified for PMS studies, physicians were advised to treat their patients as usual, without any obligation to prescribe a given drug. If the physicians chose to prescribe orlistat, they had to follow the European Prescribing Guidelines as given in the Summary of Product Characteristics. Patients (BMI \geq 28 kg/m²) in whom treatment with orlistat was indicated could be included. Patients with contraindications were excluded from the participation.

Interventions

In cases where orlistat was prescribed, the recommended regimen for all patients was orlistat (Xenical[®]) 120 mg three times daily at meal times, together with a reduced-fat diet and an increase in physical activity. The duration of orlistat treatment was at the physician's discretion. For this trial, the duration was limited to a maximum of 9 months. Visits were scheduled at base-

line, 2–4 weeks after baseline (optional) and at the end of the treatment period after about 6–9 months. The patients were informed by brochures and were advised by physicians' assistants. A specific orlistat weight management programme ('XENI-CALculated' weight reduction) was also offered as an option. This included eight 60- to 90-minute group sessions over a period of eight months, which had to be paid for by the patients. A trained dietician or physician led the groups, discussing the causes and consequences of obesity, fat-reduced diet, physical therapy, documentation of fat consumption and body weight. In addition, programme participants were trained to keep an account of their daily fat consumption with the aim of reaching a daily intake of less than 80 'fat points', preferably less than 60 'fat points' (1 'fat point' = 1 g of fat).

In each study centre, body weight to the nearest kg was determined with patients not wearing shoes and after they had passed urine. Waist circumference (measured horizontally between the lower border of the ribs and the upper border of the hip bones), hip circumference (largest circumference above the trochanter major) and body height were measured with a margin of \pm 1 cm. Blood pressure was measured following the recommendations of the International Society of Hypertension [8]. Laboratory parameters were determined at the physicians' usual laboratories.

Assessments

Based on a five-point rating scale (excellent, very good, good, moderate and inadequate), physicians assessed the effectiveness and tolerability of the treatment as well as the compliance of their patients. Patients also assessed their state of health on this scale.

Concomitant diseases were clinically diagnosed based on the German Medical Associations' criteria (diabetes mellitus: fasting blood glucose > 126 mg/dl; hypertension: systolic/diastolic blood pressure > 140/90 mmHg; dyslipidaemia: low density lipoprotein (LDL) cholesterol > 160 mg/dl, high density lipoprotein (HDL) cholesterol < 40 mg/dl and triglycerides > 200 mg/dl).

Study monitoring and data entry

Physicians entered demographic data, diagnoses, concomitant diseases and medication use, medical history and the clinical variables listed above in standardised documentation forms. On-site monitoring was performed by Hoffmann-La Roche AG field representatives, who checked the completeness of entries and collected the completed forms. Data were then entered on a separate

database and were monitored by employees of the institute responsible for data evaluation. Inconsistent or illegible data were clarified by telephone contacts with the physicians. Data entry errors were reduced by means of automated plausibility controls. For every tenth documentation form, double data entry was performed by two individuals. The error rate was always less than 1%.

Data were assessed descriptively as mean \pm standard deviation, median, minimum, maximum and absolute and relative frequencies, using the program STATISTICA Version 6.0 (StatSoft Inc.).

Results

Patients and baseline characteristics

In total, 15 549 obese patients (11 131 women and 4418 men) were included in this study (Xenical ExtraLarge study, XXL study). Most patients ($n = 15\,201$) were treated by primary health care physicians ($n = 3631$). A total of 348 patients were treated by hospital physicians ($n = 60$). Regardless of the type of physician, the median number of patients per physician was four.

The baseline characteristics of the patients are summarized in table 1. Patients were on average 48 years old and their obesity was known for an average of 13.7 years. Most patients had previously attempted to lose weight, but fewer than 10% had been able to achieve and maintain a weight loss of more than 5%.

About half of the patients had reported one or two co-morbidities, and a third had three or more co-morbidities (table 1). Hypertension was present in 41% of patients, dyslipidaemia in 34% and diabetes mellitus in 16%.

Treatment duration and compliance

Patients were treated for a mean of 7.1 months, with a follow-up visit 32 days after recruitment. In accordance with the design of a noninterventional PMS study, additional unrecorded visits could have been scheduled as deemed necessary by the physician in charge. Orlistat was used in conjunction with a reduced-fat diet in 73% of the whole patient population and/or with physical activity in 53% of all patients. One third of the patients participated in the 'XENI-CALculated' weight management programme. Only 12% of the patients used orlistat without any adjunctive measures.

For 15 138 patients (99.0%), data on weight were available at the end of the observation period. The remainder of the patients had missing single parameters, and hence, no conclusion about the number of dropouts may be inferred. A positive assessment of compliance was

Table 1 Demographic and baseline characteristics

	Treatment with orlistat	
	n	%
Women	11 131	71.6
Men	4418	28.4
Age:		
≤ 30 years	1063	6.8
30–40 years	2897	18.6
40–50 years	4646	29.9
50–60 years	4212	27.1
> 60 years	2731	17.6
Family history of obesity:		
positive	11 134	71.6
negative	3248	20.9
no information	1167	7.5
No previous therapeutical measures	4544	29.2
Presence of concomitant diseases:		
none/no information	3024	19.5
1	4289	27.6
2	3423	22.0
3	2439	15.7
4	1371	8.8
5–9	1003	6.4
Type of concomitant disease*:		
Hypertension	6331	40.7
Dyslipidaemia	5249	33.8
Diabetes	2443	15.7

*Numbers are based on the ratings of the investigators at baseline. Only those concomitant diseases for which an improvement is discussed, are given.

given by physicians for more than 80% of their patients (excellent 21.3%, very good 31.8%, good 30.0%, moderate 10.7%, inadequate 5.1% and missing 1.1%).

Body weight reduction and overall effectiveness of orlistat

Between the start and end of the study, a mean weight loss of 10.7% was achieved. Men experienced a higher absolute decrease in weight, but the percentage change was comparable for both men and women. The positive effect on body weight resulted in an overall mean BMI decrease of 3.76 kg/m². Reductions were also obtained for waist and hip circumferences (table 2).

87% of patients lost at least 5% of their baseline weight and 50% of patients reduced their body weight by at least 10% (figure 1). The best weight reductions ($-12.0\% \pm 5.8\%$) were obtained for those patients who were treated with orlistat and who used all adjunctive measures, i.e. participation in the 'XENI-CALculated' programme together with a reduction in fat intake and increased physical activity. As expected, patients treated with orlistat only, without any adjunctive measure,

Table 2 Effect of orlistat on body weight, body mass index (BMI), waist circumference and hip circumference for all patients and by gender

	All patients (n=15 138)				Women (n=10 815)		Men (n=4323)	
	Before treatment	After treatment	Absolute change* (Mean±SD)	Mean change (%)	Absolute change* (Mean±SD)	Mean change (%)	Absolute change* (Mean±SD)	Mean change (%)
Body weight (kg)	99.2	88.5	-10.78 ± 6.94	-10.7	-10.30 ± 6.51	-10.7	-11.96 ± 7.8	-10.7
BMI (kg/m ²)	34.7	31.0	-3.76 ± 2.38	-10.7	-3.75 ± 2.36	-10.7	-3.78 ± 2.43	-10.7
Waist circumference† (cm)	114.6	106.6	-8.24 ± 8.37	-7.0	-7.91 ± 8.42	-6.9	-9.02 ± 8.19	-7.2
Hip circumference‡ (cm)	116.4	110.6	-6.18 ± 7.17	-5.1	-6.55 ± 7.09	-4.4	-5.30 ± 7.28	-5.4

*p < 0.0001 for differences between start and end of study for all parameters.

†n (women) = 8036, n (men) = 3342.

‡n (women) = 7723, n (men) = 3240.

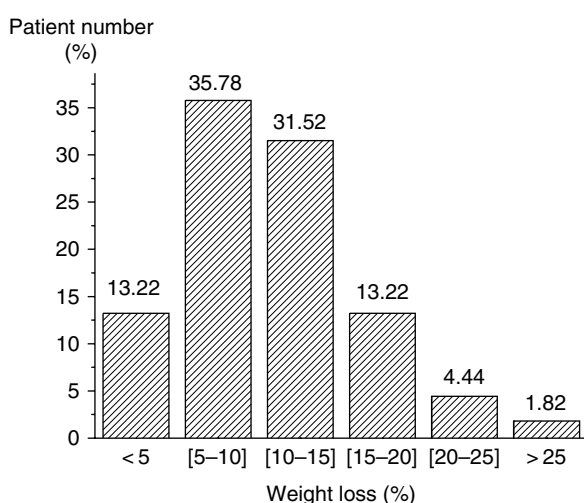


Fig. 1 Categorical weight loss after treatment with orlistat

achieved the least treatment benefit, but still achieved an average weight reduction of $-9.4\% \pm 7.5\%$. Intermediate results were obtained for the various other treatment combinations given (table 3).

For the majority of their patients (86.5%), physicians assessed the effectiveness of treatment as positive (good 30.9%, very good 33.5% and excellent 22.1%). For 8.7% of patients, the effectiveness of treatment was assessed as moderate, and for 4.2%, it was unsatisfactory. No information on the effectiveness of treatment was given for 0.5% of patients.

Influence on co-morbidities

Orlistat exerted a positive influence on blood lipids, blood pressure and blood glucose. On average, a marked improvement of the lipid profile was achieved (figure 2A). The decrease in LDL cholesterol and the increase in HDL cholesterol led to a mean decrease of 15.4% in the LDL/HDL ratio. The mean systolic/diastolic blood pressure was reduced by 8.7/5.1 mmHg (figure 2B) and the mean heart rate decreased by 3.0 beats per minute. Overall, a decrease of 7.5% in blood glucose was observed (figure 2C).

The beneficial effects were particularly apparent in patients with obesity-related co-morbidities. For patients with dyslipidaemia, there were marked reductions in total

Table 3 Reduction in body weight with respect to adjunctive measures

Adjunctive measure				n*	Body Weight		
None	Reduced-fat diet	Physical activity	'Xeni-calculated' programme		(Kg, mean ± SD)	Before	After
No	No	No	Yes	795	98.6 ± 17.3	87.9 ± 16.3	-10.8 ± 5.8
No	No	Yes	No	627	98.1 ± 16.7	87.7 ± 15.9	-10.6 ± 6.0
No	No	Yes	Yes	388	98.7 ± 16.7	87.7 ± 15.1	-11.1 ± 5.2
No	Yes	No	No	2659	99.0 ± 17.9	89.5 ± 16.6	-9.5 ± 5.9
No	Yes	No	Yes	1163	100.7 ± 17.8	90.0 ± 16.2	-10.5 ± 5.2
No	Yes	Yes	No	4142	99.1 ± 17.0	87.7 ± 15.3	-11.4 ± 5.6
No	Yes	Yes	Yes	2682	99.2 ± 17.9	87.1 ± 15.9	-12.0 ± 5.8
Yes	No	No	No	1856	99.1 ± 17.8	89.7 ± 17.3	-9.4 ± 7.5

*For n = 189 patients, no information about adjunctive measures was available; for n = 637 patients, various combinations with other programmes were given.

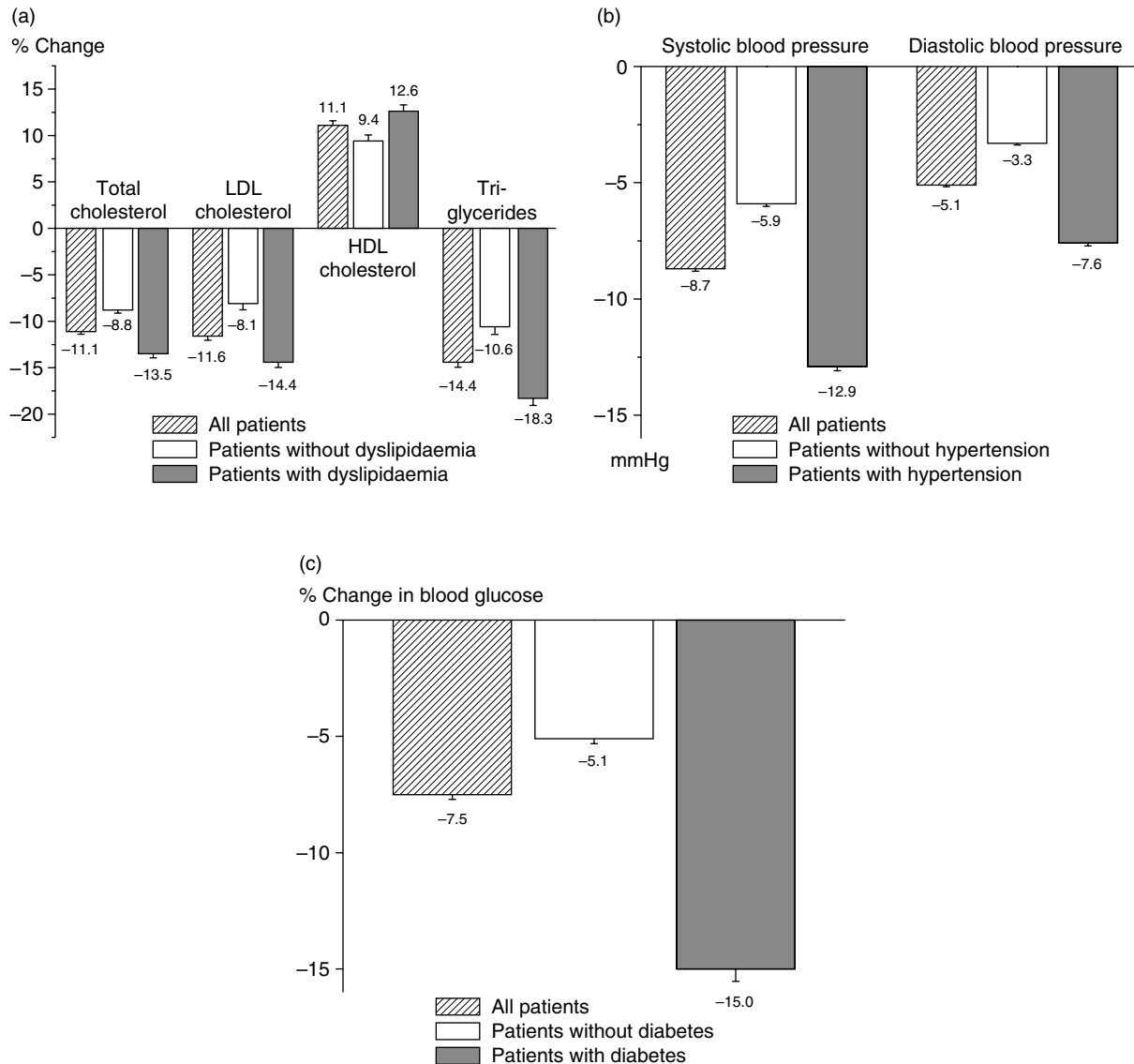


Fig. 2 Beneficial effect of treatment with orlistat on blood lipids, blood pressure and blood glucose. (A) Change in blood lipids (%; \pm SEM); (B) Change in blood pressure (mmHg, \pm SEM); (C) Change in blood glucose (%; \pm SEM). $p < 0.0001$ for all changes from baseline

cholesterol (14%), LDL cholesterol (14%) and triglycerides (18%) whereas HDL cholesterol levels increased by 13% (figure 2A). For patients with hypertension, the mean systolic blood pressure decreased from 155.0 mmHg at the start of the study by 12.9 mmHg to 142.1 mmHg after the 7-month observation period. Correspondingly, mean diastolic blood pressure decreased from 92.2 to 84.6 mmHg (figure 2B). Patients with diabetes had an average baseline blood glucose level of 155 mg/dl, which was reduced by 15% at the end of the study (figure 2C).

A number of patients were able to stop or reduce the intake of concomitant medications: 31% of patients with

dyslipidaemia stopped their intake of lipid-lowering medications and a further 15% had a reduction of the dosage. Moreover, 18% of those patients reporting hypertension stopped their antihypertensive treatment and 8% had a dosage reduction. For those patients with diabetes, 16% stopped their medication and 18% reduced the dosage.

Tolerability of orlistat

Overall, orlistat was considered by the investigators to have a good tolerability for more than 90% of patients

(excellent 21.3%, very good 34.4%, good 36.7%, moderate 5.4%, inadequate 1.3% and missing 1.0%). The good tolerability of orlistat was also indicated by the assessment of the patients' general state of health. At their final examination, 88.7% of patients reported a good, very good or an excellent state of health compared with only 40.4% before the start of treatment. A moderate or unsatisfactory state of health was reported by only 9.4% of patients after their treatment compared with 59.0% before the start of treatment. In total, 65.1% of patients had an improvement of their state of health, 33.4% reported no change and only 1.5% had a deterioration.

Adverse events were reported in 1.5% of patients ($n = 234$) and were mainly disorders of the gastrointestinal system. Diarrhoea or liquid stools ($n = 64$), fatty stools ($n = 50$), flatulence ($n = 23$) and nausea ($n = 7$) were the most frequently reported adverse events. Headaches were reported by six patients; reports of all other adverse events were given by four patients or fewer. After the end of the study, more than half of the patients (62.2%) planned to continue their treatment with orlistat.

Discussion

This was the largest naturalistic study with orlistat in obese patients, confirming the effectiveness of orlistat in conjunction with lifestyle changes previously shown in several controlled trials [3,6,9] and during routine practice [10]. The weight reduction obtained in this PMS study (10.7%; 10.8 kg) was considerable and comparable with results of controlled studies on orlistat in conjunction with intensive lifestyle interventions [3,9]. A total of 87% of the patients had a weight reduction of at least 5% and 51% had a weight loss of at least 10%; no difference was detectable between women and men. These results show that in general practice, orlistat treatment of obese patients in conjunction with lifestyle changes is as effective as treatments provided by special care centres, which incur large expenditures on nonmedicinal therapies.

As the purpose of this PMS study was to evaluate the effectiveness of orlistat under naturalistic 'real-life' conditions rather than the drug efficacy, as done in controlled clinical trials, physicians were free to advise their patients on adjunctive measures. Slight differences in body weight reduction were observed depending on the extent of patient adherence to other measures adjunctive to the use of orlistat. As expected, those patients who participated in the 'XENI-CALculated' programme and observed the recommended reduced-fat diet in combination with increased physical activity, achieved the greatest reduction in body weight (12.0%). For those patients

who reported participation in this programme but did not reduce their fat consumption or increase their physical activity, lower weight reductions of 10.5%–11.1% were obtained. Considerable weight reductions were still achieved in those patients who were treated with orlistat with no adjunctive measures (9.4%), and who also adopted a fat-reduced diet (9.5%) or increased their physical activity (10.6%).

The reduction in body weight was similar in patients with (10.1%) and those without (10.7%) diabetes. In trials performed so far, patients without diabetes generally achieved greater reductions in body weight (–10.3 kg) [3] than those with diabetes and who were treated orally (–4.6 kg) or were on insulin (–6.2 kg) [4,11]. Similar differences in weight loss between diabetic and nondiabetic patients have been shown with sibutramine treatment [12,13] and in weight loss regimens without antiobesity drugs [14]. In order to compare the effectiveness of orlistat in diabetic and nondiabetic patients, the present study included a sufficient number of diabetic patients to provide a reliable data output. A clinically meaningful improvement of the glycaemic control was reached in diabetic patients with a decrease in blood glucose levels of 27 mg/dl (15.0%).

The changes in blood lipids were impressive, especially in patients with dyslipidaemia. Total cholesterol and LDL cholesterol were both reduced by 14%, HDL cholesterol was increased by 13% and the atherogenic ratio LDL/HDL improved by 18%. These results are comparable with those of a previous controlled trial performed in patients with dyslipidaemia [15].

Systolic and diastolic blood pressures were also significantly reduced. A meta-analysis of randomised placebo-controlled trials in 628 obese patients with hypertension concluded that a reduction of 9.4 mmHg and 7.7 mmHg for the systolic and diastolic blood pressure, respectively, may be expected with orlistat treatment in conjunction with lifestyle changes [16]. As in the present study, the heart rate decreased by three beats per minute, and the product of systolic blood pressure and frequency, an important determinant of myocardial oxygen consumption, decreased by an average of 10% [16].

The improvements in cardiovascular risk factors were accompanied by a reduction in the medications necessary to treat the concomitant diseases. Approximately one sixth of obese patients with hypertension or with diabetes stopped the intake of antihypertensive treatments or oral antidiabetic medications, respectively. In patients with dyslipidaemia, one in three patients stopped the intake of lipid-lowering agents. It should be noted that neither the investigators nor the patients were specifically instructed in the study

protocol to reduce concomitant medications. Thus, orlistat treatment would be expected to lead to considerable savings in costs of medications for obesity-related diseases although this has not yet been formally analyzed.

The number of adverse events reported by the patients was remarkably small and considerably lower than those reported in previous controlled studies. This difference may be explained by the method used for collecting the data, because in PMS studies, patients report these events only spontaneously. Furthermore, because of the nature of PMS studies, detailed data are unavailable for patients prematurely terminating their treatment with orlistat. It is possible that for some of these patients, side-effects could have been the reason for discontinuation of treatment.

Conclusion

The current study presents the results of the largest naturalistic study undertaken of orlistat therapy in a large number of overweight and obese patients, and shows that co-morbidities may be improved effectively under everyday real-life conditions in general practice. The data confirm that body weight reductions and improvements of cardiovascular risk factors are comparable with the outcomes reported from randomised, controlled trials. Therefore, treatment of obesity may be entrusted to general practitioners without any loss in the quality of treatment compared with results seen in special care centres.

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