

References

Anderson JW, Schwartz SM, Hauptman J et al. Low-dose orlistat effects on body weight of mildly to moderately overweight individuals: a 16 week, double-blind, placebo-controlled trial. *Ann Pharmacother* 2006; **40**: 1717-1723.

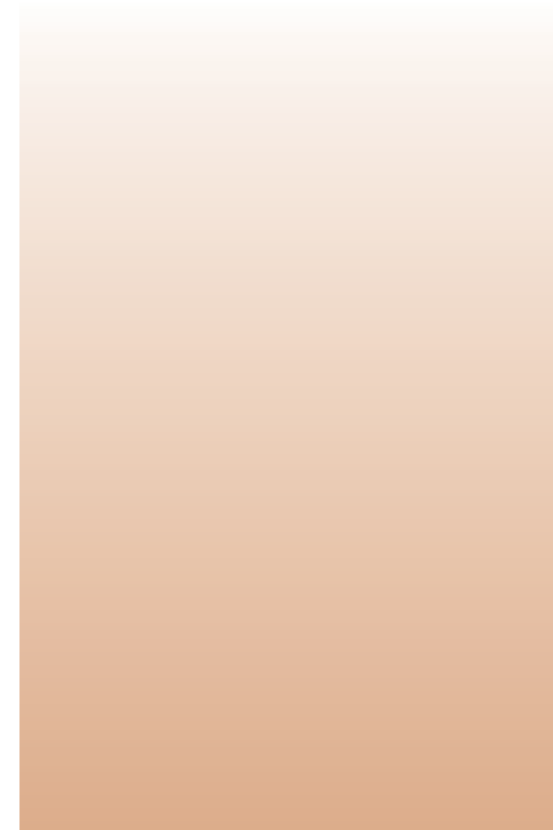
Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR. Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med* 2000; **9**: 160-167.

Rossner S, Sjostrom L, Noack R, Meinders AE, Nosedá G. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European Orlistat Obesity Study Group. *Obes Res* 2000; **8**: 49-61.

Schwartz SM, Bansal VP, Hale C, Rossi M, Engle JP. Compliance, behavior change, and weight loss with orlistat in an over-the-counter setting. *Obesity Res* 2008; **16**: 623-629.

Orlistat for the management of overweight individuals and obesity: a review of potential for the 60 mg, over-the-counter dosage

7008588



Published

Expert Opinion on Pharmacotherapy 2007; **8**: 1733-42

Authors

Anderson JW



alli is a registered trademark of the GlaxoSmithKline group of companies

Aims of the study

Review article with US focus. Topics covered:

- Overview of weight loss treatments (in development and marketed, flagging importance of non-prescription [over-the-counter, OTC] availability)
- Pharmacodynamics and pharmacokinetics
- Clinical efficacy (Phase III studies, Rossner, Hauptman, Anderson, Schwartz)
- Summary of safety.

Treatments being studied

Orlistat 60 mg

Treatment period

Phase III studies duration of treatment ranged from 3 months (Schwartz) to 2 years (Rossner, Hauptman)

Details of study methods and results

- See Clinical Summaries for Rossner, Hauptman and Schwartz studies
- Note that this review includes data from a study by Anderson in subjects with BMI 25-28
- It is recommended that the underlying references (see text of publication) are used to support key statements rather than simply citing this review article.

Introduction

- Orlistat is a highly lipophilic hydrogenated derivative of lipostatin, a natural product from *Streptomyces toxytricini*
- Orlistat 60 mg was approved by the FDA for OTC use in the US in February 2007. It is indicated for overweight adults who are ≥ 18 years of age.

Pharmacodynamics and pharmacokinetics

- Orlistat is a reversible lipase inhibitor that acts locally in the stomach and small intestine. It is unlike any other available weight-loss medication
- This unique mode of action is of particular benefit to consumers since orlistat does not act in the central nervous system (CNS) and is not addictive
- Orlistat is minimally absorbed systemically (< 2%), and does not accumulate following long term administration
- Orlistat 60 mg inhibits absorption of ~ 25% of ingested fats, compared with ~ 30% for orlistat 120 mg. Hence, orlistat 60 mg has ~ 85% the efficacy of the 120 mg dose
- Orlistat has a limited dose-response effect. Studies in healthy volunteers have shown that the maximum amount of fat excreted in the faeces following a 400 mg/day dose to be 32% of the dietary fat intake. Doses > 400 mg/day had no additional effect
- Orlistat has a short plasma half-life of 1–2h. It is metabolised in the intestinal wall to yield two pharmacologically inactive metabolites
- Based on studies with orlistat 120 mg, 97% of orlistat is excreted in the faeces (83% unchanged), with complete elimination within 3–5 days. Plasma concentrations were minimal even when doses of up to 800 mg were administered (single-dose). This finding was also supported in multiple-dose studies in which patients received up to 400 mg 3 times a day.

Clinical efficacy*

- All of the controlled clinical studies demonstrate that orlistat 60 mg 3 times a day consistently provided significantly greater weight loss than diet alone, regardless of the level of dietary intervention or degree of overweight. The weight losses achieved were similar to those seen with 120 mg.

Safety and tolerability

- Orlistat's mode of action results in increased faecal fat excretion, therefore, gastrointestinal (GI) adverse events (AEs) would be expected to occur more frequently in orlistat-treated subjects than in placebo-treated subjects
- For most GI adverse events, the incidence was 20–30% lower in the 60 mg group than in the 120 mg group
- With the exception of the GI system, the incidence of AEs was similar with orlistat 60 mg compared with placebo across all of the studies presented
- Overall, the safety profile of orlistat 60 mg is similar to that seen with the 120 mg dose. However, the orlistat 60 mg dose provides improved tolerability
- Orlistat was generally well tolerated during long term use. Most GI events occurred early during treatment (within the first 12 weeks) and were:
 - limited to one or two episodes per subject
 - mild-to-moderate in severity
 - transient, in that they resolved without intervention within 1–4 weeks
- People who exceed the recommended fat intake (> 30% of calories from fat; in a 2000 kcal/day diet, this equates to < 67 g of fat) are more likely to experience more frequent and intense GI events
- Maintaining a dietary fat intake of < 60 g/day has been shown to decrease the likelihood of developing GI adverse effects
- The educational tools and support programme provided with non-prescription orlistat 60 mg have been designed to help individuals to limit fat intake and maintain appropriate dietary changes to maximise success
- There are very few drug interactions associated with orlistat. The EU SPC lists ciclosporin, oral anticoagulants, oral contraceptives, fat soluble vitamins, acarbose and amiodarone
- There is no evidence that orlistat has any effect on the CNS that is indicative of abuse potential
- Systemic exposure to orlistat is minimal and plasma levels of orlistat even after 2 years of continual treatment were extremely low
- Orlistat has a low potential for misuse and abuse
- The benefits of treatment with orlistat 60 mg far exceed the risks.

Expert Opinion

- Orlistat 60 mg has the potential to make an important contribution to weight management
- Successful weight loss and long term weight management require lifestyle changes. Increased physical activity, lower dietary fat intake and more vegetable and fruit consumption are essential. These health-promoting behaviour changes require daily reinforcement. Developing routines that support appropriate food choices are very important for weight management
- Taking one orlistat capsule three times daily with meals is one practice that has the potential to substantially modify eating behaviour
- Using orlistat 60 mg as a tool to reinforce lifestyle changes has the potential to promote successful weight loss and long term weight maintenance
- With effective communication with healthcare providers and consumers, orlistat has the potential to have a substantial effect on weight management in adults
- Non-prescription orlistat may have a major impact on the consumer market for obesity products.

*As in the original publications, weight loss data presented are based on change from start of the placebo lead-in. In the **alli** submissions, data were analysed based on change from start of the double-blind treatment period. For this reason, efficacy data presented in the SPC, for instance, do not match the published data