Inhibition of Digestive Lipase by Orlistat for the Treatment of Obesity

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Obesity is a serious disease which predisposes to numerous health problems, including diabetes, hypertension and atherosclerosis. It accounts for 2-7% of the total healthcare costs in Western countries and its prevalence is increasing rapidly in Europe. Dietary therapy is the first line treatment for obesity, but it is not sufficient in many cases and drug therapy also has to be considered.

Anti-obesity treatments based on the use of digestive lipase inhibitors were therefore developed to reduce dietary fat absorption. Orlistat (also known as tetrahydrolipstatin), is a potent covalent inhibitor of digestive lipases, derived from lipstatin a natural product of *Streptomyces toxytricini*. Orlistat is an active site-directed inhibitor which reacts with the nucleophilic serine residue from the catalytic triad of human gastric (HGL) and pancreatic (HPL) lipases. Orlistat was the first lipase inhibitor introduced on the market in 1998 (EU) and in 1999 (US) as a weight loss inducer for the treatment of obesity. It is the first anti-obesity drug (trade name Xenical® by Roche and more recently over-the-counter as Alli® by GlaxoSmithKline) used today with annual sales of more than 400 million US dollars.

Collaborating with Roche during almost 15 years, our laboratory studied the physico-chemical properties of Orlistat as well as in vitro lipases inhibition. We thus performed the first clinical study which allowed quantifying the in vivo respective inhibition of HGL and HPL and the corresponding decrease in gastrointestinal lipolysis.

In this presentation I will report a general overview of these works, and discuss the mode of action of Orlistat.

References: