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EDITORIAL

# Dirlotapide, a U.S. Food and Drug Administration-Approved First-in-Class Obesity Drug for Dogs—Will Humans Be Next?

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On January 5, 2007 the U.S. Food and Drug Administration (FDA) approved the diet drug dirlotapide (Slentrol, Pfizer Inc., New York, NY) for dogs. The Slentrol package insert carries special warnings about its side effects when used by humans, including the wording "not for use in humans." If inappropriately used by humans, the drug can cause abdominal distention, abdominal pain, diarrhea, flatulence, headache, increased serum transaminases, nausea, and vomiting. The product is intended for dogs that are at least 20% overweight.[1]

Centers for Disease Control and Prevention use body mass index (BMI) as a screening tool for populations to identify weight problems in adults. BMI is a number calculated from a person's weight and height. A normal BMI is 18.5–24.9, an overweight BMI is 25.0–29.9, and an obese BMI is 30.0 or greater. A human who is more than 20% overweight will have a BMI of 30 or greater (because the BMI will be at least 20% greater than 25) and the person will be defined as obese by the BMI classification. A dog that is 20% overweight will be deemed sufficiently obese to be a candidate for dirlotapide.

Surveys have found that 5% of dogs are obese[2] and 35% are overweight.[3] Two teams from Centers for Disease Control recently reported the incidence of obesity in U.S. adults during the period of 2003–2004. In one study, 32% of this population was obese and an additional 32% of the population was overweight.[4] In the other study the mean waist circumference and prevalence of abdominal obesity were noted to have increased continuously since the early 1990s, such that over half of the study population had abdominal obesity.[5] There will likely be a market for an obesity drug for dogs, just as there is currently one for humans.

Dirlotapide is the first FDA-approved product in a new class of drugs called selective microsomal triglyceride transfer protein (MTP) inhibitors (**Figure 1**). These types of agents block the assembly and release of lipoproteins into the bloodstream.[6] The mechanism for the weight loss associated with dirlotapide is not completely understood but is thought to result from reduced fat absorption along with a satiety signal from lipid-filled cells lining

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**Abbreviations:** (BMI) body mass index, (FDA) U.S. Food and Drug Administration, (LDL) low-density lipoprotein, (MTP) microsomal triglyceride transfer protein

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the intestine. MTP is essential for the synthesis of both chylomicron in the intestine and very low-density lipoprotein (LDL) in the liver.[7] The drug reduces appetite and increases fecal fat.[1] Dirlotapide is not marketed as a cure for obesity. The decreased appetite experienced when dogs are treated with this drug is temporary and lasts no longer than 1–2 days beyond the cessation of therapy. The safety of dirlotapide use in dogs has not been evaluated beyond 1 year of therapy.

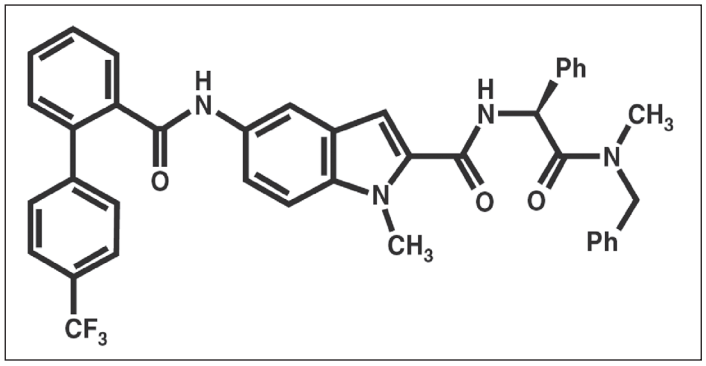


**Figure 1.** Chemical structure of dirlotapide.

Dirlotapide is supplied as an oral solution for once-daily dosing. This drug has a mean elimination half-life of 5–18 hours that increases with prolonged administration. The recommended treatment regimen consists of an initial weight-dependent dose during the first 14 days and a second (higher) weight-dependent dose during the second 14 days, if the first dose is tolerated. Later, the veterinarian care provider is advised to assess the dog's progress at monthly intervals and to adjust the dose as needed (up to a dose ceiling), based on the amount of weight lost. After the dog has achieved the goal weight, then the drug's manufacturer recommends continued use of the drug for 3 months, during which time the veterinarian and the dog owner determine the optimal level of food intake and physical activity necessary to maintain the dog's weight. The most frequent side effects in dogs include vomiting, loose stools, diarrhea, lethargy, anorexia, and elevations in serum transaminase levels. No significant decreases in fat-soluble vitamin levels from dirlotapide therapy have been noted in dog studies,[6] but deficiencies of these substances have been noted in disorders of lipoprotein synthesis.[8]

In one study reported by the manufacturer in the drug's package insert but not referenced to an article, a 4-month course of dirlotapide therapy in obese dogs resulted in a statistically significant mean weight loss of 11.8%.[1] No long-term studies have reported the efficacy of this drug in obese humans.

In another study,[9] a different MTP inhibitor (BMS 201038) was administered to a cohort of six subjects with familial hypercholesterolemia to reduce LDL production and lower serum cholesterol levels. The subjects' initial mean BMI was high-normal at 24.8. After 4 weeks of therapy, the subjects' weights fell by a mean 4.4% ($p = 0.06$) and the weights returned to baseline following a 4-week washout period. This treatment reduced plasma LDL cholesterol levels by up to 50% and triglyceride levels by up to 65%, and had no clinically significant effects on high-density lipoprotein cholesterol levels. Steatorrhea was controlled by the restriction of dietary fat and dosage adjustments.[9] Elevated aminotransferase levels occurred in four of six of the subjects, and magnetic resonance imaging-documented elevations of hepatic fat occurred in every subject. These enzyme and fat abnormalities returned to normal within 4 weeks of discontinuing the drug, except for one subject in whom the hepatic fat accumulation resolved after 14 weeks. The investigators expressed concern that the aminotransferase elevations and steatosis were potentially serious adverse events that should not be underestimated and recommended long-term studies of MTP inhibitors under carefully monitored conditions to fully determine the safety of these agents.

There is precedent for the use of fat-blocking agents to treat obesity. Orlistat, which is marketed as a prescription drug, Xenical® (Roche, Basel, Switzerland), and as an over-the-counter product, Alli™ (GlaxoSmithKline, Brentford, United Kingdom), is a drug designed to treat obesity by inhibiting pancreatic lipase and preventing triglycerides from the diet from being hydrolyzed and absorbed. The result is that triglycerides are excreted undigested in the feces.[10] Dirlotapide also blocks fat absorption, which leads to weight loss.

New illegal veterinary drugs are produced and distributed on the black market continuously. Given the current limited state of knowledge about dirlotapide, it would be dangerous and foolish for a bodybuilder or an obese person to obtain this drug from a black market source in order to decrease body fat percentage or lose weight.[11]

Microsomal triglyceride transfer protein inhibitors may play a future role in the treatment of hyperlipidemias in patients with type 2 diabetes, metabolic syndrome, and familial hyperlipidemias.[12] If the safety and tolerability issues reported with MTP inhibitor therapy in dogs and humans can be overcome, then dirlotapide might prove to be a viable alternate therapy for obesity for people unwilling or unable to comply with a hypocaloric diet and regular exercise.

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