

More Weight Lost With Liraglutide Than Orlistat

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Senior Editor

PHOENIX — Liraglutide, an investigational drug given once a day, produced significantly more weight loss than orlistat in a randomized, 20-week, placebo-controlled trial in obese patients, most of whom were not diabetic.

Participants on four different doses of liraglutide—1.2, 1.8, 2.4, and 3.0 mg—

tested in the study lost significantly more weight, compared with a control group on placebo. Those treated at the two highest doses (2.4 and 3.0 mg per day) lost significantly more weight than did those given 120 mg of orlistat (Xenical) three times a day.

The mean weight loss ranged from 4.8 kg with the lowest 1.2-mg dose of liraglutide to 7.2 kg with the 3.0-mg dose, according to the investigators. The mean

weight loss for placebo was little more than 2 kg and about 4 kg with orlistat.

“A very nice dose separation” was how Dr. Arne Astrup, the lead author and head of the department of human nutrition at the University of Copenhagen, described results of the six-arm, 564-patient study at the annual scientific meeting of NAASO, the Obesity Society.

Novo Nordisk A/S sponsored the trial. It announced in May that it had sub-

mitted a New Drug Application for liraglutide to the U.S. Food and Drug Administration and a marketing authorization application to the European Medicines Agency—both seeking an indication for liraglutide in the treatment of people with type 2 diabetes. These were followed in July by a request for marketing approval in Japan.

Liraglutide is a human analogue of glucagon-like peptide-1 (GLP-1). According to the company's Web site, liraglutide inhibits appetite and stimulates insulin production only when glucose levels become too high.

In September, *The Lancet* published the results of a 1-year phase III trial showing that patients with early type 2 diabetes achieved better glycemic control with liraglutide monotherapy (doi: 10.1016/S0140-6736(08)61246-5).

Nearly two-thirds of the participants in the current study did not have diabetes; most of the rest were classified with prediabetes, leaving about 3% with the disease. About three-quarters of the population were women, and the average age



The proportion who lost 5% or more of body weight was 44% with orlistat but 54%-76% with liraglutide.

DR. ASTRUP

was in the mid-40s (range 18-65 years). Body mass index ranged from 30 kg/m² to 40 kg/m² and weight from about 96 kg to 98 kg. The protocol encouraged all participants to go on a reduced-calorie diet and be physically active.

The proportion of participants who lost 5% or more of body weight was 44% with orlistat but ranged from 54% to 76% with the liraglutide doses; and 28% of those on the highest dose lost more than 10% of their body weight. Waist circumference also went down significantly relative to placebo at the two highest liraglutide doses.

Pulse rates increased by up to four beats per minute with liraglutide but declined with placebo and orlistat. Mean systolic blood pressure decreased 5.6-8.8 mm Hg in the liraglutide groups, and declined 4 mm Hg with placebo and 5.4 mm Hg with orlistat.

Four patients had hypoglycemic symptoms with liraglutide. None required assistance. The most common events were nausea and vomiting. “In all the doses except the highest, [nausea] came down to the placebo level over time,” Dr. Astrup said. A phase III trial is planned.

Dr. Astrup disclosed being a consultant to Novo Nordisk and receiving financial support for serving on advisory boards relative to liraglutide. The investigators also included Novo Nordisk employees, one of whom was a shareholder in the company, and other scientists who had received financial support and/or served on advisory boards. ■

BRIEF SUMMARY - Consult full prescribing information before use.

Tussicaps®
(Hydrocodone Polistirex and Chlorpheniramine Polistirex)
Extended-Release Capsules

Rx only

CONTRAINDICATIONS

Tussicaps® extended-release capsules are contraindicated in patients with a known allergy or sensitivity to hydrocodone or chlorpheniramine.

The use of Tussicaps® extended-release capsules are contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression.

WARNINGS

Respiratory Depression – As with all narcotics, Tussicaps® extended-release capsules produce dose-related respiratory depression by directly acting on brain stem respiratory centers. Hydrocodone affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. Caution should be exercised when Tussicaps® extended-release capsules are used postoperatively and in patients with pulmonary disease, or whenever ventilatory function is depressed. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated (see **OVERDOSAGE**).

Head Injury and Increased Intracranial Pressure – The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions, which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions – The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Obstructive Bowel Disease – Chronic use of narcotics may result in obstructive bowel disease especially in patients with underlying intestinal motility disorder.

Pediatric Use – The use of Tussicaps® extended-release capsules are contraindicated in children less than 6 years of age (see **CONTRAINDICATIONS**).

In pediatric patients, as well as adults, the respiratory center is sensitive to the depressant action of narcotic cough suppressants in a dose-dependent manner. Caution should be exercised when administering Tussicaps® extended-release capsules to pediatric patients 6 years of age and older. Overdose or concomitant administration of Tussicaps® extended-release capsules with other respiratory depressants may increase the risk of respiratory depression in pediatric patients. Benefit to risk ratio should be carefully considered, especially in pediatric patients with respiratory embarrassment (e.g., croup) (see **PRECAUTIONS**).

PRECAUTIONS

General

Caution is advised when prescribing this drug to patients with narrow-angle glaucoma, asthma, or prostatic hypertrophy.

Special Risk Patients – As with any narcotic agent, Tussicaps® extended-release capsules should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Information for Patients

As with all narcotics, Tussicaps® extended-release capsules may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly. Tussicaps® extended-release capsules must not be diluted with fluids or mixed with other drugs as this may alter the resin-binding and change the absorption rate, possibly increasing the toxicity.

Keep out of the reach of children.

Cough Reflex – Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when Tussicaps® extended-release capsules are used postoperatively, and in patients with pulmonary disease.

Drug Interactions

Patients receiving narcotics, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants

(including alcohol) concomitantly with Tussicaps® extended-release capsules may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

The concurrent use of other anticholinergics with hydrocodone may produce paralytic ileus.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity and reproductive studies have not been conducted with Tussicaps® extended-release capsules.

Pregnancy

Teratogenic Effects. Pregnancy Category C – Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. Tussicaps® extended-release capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects – Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

Labor and Delivery

As with all narcotics, administration of Tussicaps® extended-release capsules to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Tussicaps® extended-release capsules, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The use of Tussicaps® extended-release capsules are contraindicated in children less than 6 years of age (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Respiratory, Thoracic and Mediastinal Disorders**).

Tussicaps® extended-release capsules should be used with caution in pediatric patients 6 years of age and older (see **WARNINGS, Pediatric Use**).

Geriatric Use

Clinical studies of hydrocodone polistirex and chlorpheniramine polistirex extended-release did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Gastrointestinal Disorders

Nausea and vomiting may occur; they are more frequent in ambulatory than in recumbent patients. Prolonged administration of Tussicaps® extended-release capsules may produce constipation.

General Disorders and Administration Site Conditions

Death

Nervous System Disorders

Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, euphoria, dizziness, psychic dependence, mood changes.

Renal and Urinary Disorders

Ureteral spasm, spasm of vesical sphincters, and urinary retention have been reported with opiates.

Respiratory, Thoracic and Mediastinal Disorders

Dryness of the pharynx, occasional tightness of the chest, and respiratory depression (see **CONTRAINDICATIONS**). Tussicaps® extended-release capsules may produce

dose-related respiratory depression by acting directly on brain stem respiratory centers (see **OVERDOSAGE**). Use of Tussicaps® in children less than 6 years of age has been associated with fatal respiratory depression. Overdose with Tussicaps® extended-release capsules in children 6 years of age and older, in adolescents, and in adults has been associated with fatal respiratory depression.

Skin and Subcutaneous Tissue Disorders

Rash, pruritus.

DRUG ABUSE AND DEPENDENCE

Tussicaps® extended-release capsules are Schedule III narcotics. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; therefore, Tussicaps® extended-release capsules should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when Tussicaps® extended-release capsules are used for a short time for the treatment of cough. Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued oral narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy.

OVERDOSAGE

Signs and Symptoms – Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. Although miosis is characteristic of narcotic overdose, mydriasis may occur in terminal narcosis or severe hypoxia. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur. The manifestations of chlorpheniramine overdose may vary from central nervous system depression to stimulation.


Treatment – Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdose or unusual sensitivity to narcotics including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone in this formulation may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

A Schedule CIII Narcotic.

For Medical Information

Contact: Product Monitoring Department
Phone: 800-778-7898

Manufactured by:
Mallinckrodt Inc.
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