

drug information perspectives

Volume 31 (2) 2011

Editor and author:

Barbara Cadario, BSc(Hon), BScPhm., MSc

Chairman, Medical Review

Laird Birmingham, MD, MHSc, FRCP(C)

LIRAGLUTIDE

SYNONYM: NN2211

TRADE NAME: Victoza

CLASSIFICATION

- GLP-1 receptor agonist
- GLP-1 analog
- Hypoglycemic agent

ACTION

- A full agonist at the GLP-1 receptor.
- Lowers blood glucose levels by increasing glucose-dependent insulin secretion, decreasing hepatic glucose production, and delaying gastric emptying.
- A synthetic recombinant derivative of GLP-1, with one amino acid substitution (97% homology) and a fatty acid side chain. GLP-1 is an incretin (INtestinal seCRETion of INSulin) peptide that produces glucose-dependent stimulation of insulin release from pancreatic beta cells, decreases plasma glucagon levels, delays gastric emptying, and reduces hunger and food intake. Oral intake of carbohydrate and fat normally results in secretion of GLP-1 from the intestine. Patients with Type 2 diabetes mellitus (T2DM) have an impaired GLP-1 response to food and consequently less insulin secretion.
- In T2DM, liraglutide increases glucose-dependent secretion of insulin from pancreatic beta cells (when glucose levels are at or above 6-7mmol/L), lowers circadian plasma glucose including nocturnal glucose by 2mmol/L, lowers postprandial plasma glucose by 20%, decreases plasma glucagon levels (both fasting and meal-related), slows gastric emptying (peak is delayed by 15 minutes), and produces a dose-dependent weight loss. However, insulin sensitivity is usually unchanged, and insulin secretion does not reach levels seen in non-diabetic subjects. In rodents, liraglutide decreases food and water intake.
- In animals, GLP-1 stimulates beta cell proliferation and inhibits beta cell apoptosis. Liraglutide stimulates beta cell and non-beta cell proliferation, and increases beta cell mass in rodents. In humans, liraglutide improves HOMA-B (an indicator of beta cell function) by 30% and inhibits beta-cell apoptosis *in vitro*. Some preliminary data suggest there is proliferation of beta cells and inhibition of apoptosis *in vitro* when human beta cells are incubated with liraglutide; the clinical significance is unknown.

B.C. Drug and Poison Information Centre

655 West 12th Avenue, Vancouver, BC V5Z 4R4
Phone: (604) 707-2789; Fax: (604) 707-2807

PHARMACOKINETICS

Half-life: 13 hours after subcutaneous injection. The long half-life is due to high albumin binding (the fatty acid side chain promotes slow absorption from the injection site; binding to albumin reduces glomerular filtration), and slow metabolism by DPP-4.

Absorption: Slowly absorbed after subcutaneous injection (T_{max} 9-14 hours) with bioavailability 55%.

Distribution: Highly bound to plasma protein (99%). Small V_d.

Metabolism: Mainly degraded in the body into small peptides, amino acids, and fatty acid fragments. Metabolized by DPP-4 and neutral endopeptidases more slowly than GLP-1.

Elimination: No intact liraglutide detected in urine or feces. Some minor metabolites appear in urine (6% of a dose) and feces (5% of a dose).

Special populations:

- **Elderly:** No change in pharmacokinetics.
- **Hepatic impairment:** In severe impairment, AUC is decreased 44%.
- **Renal impairment:** Decreased AUC in mild (35%), moderate (19%), severe (29%), and End Stage Renal Disease (30%). No liraglutide detected in dialysis fluid.
- **Sex difference:** AUC and C_{max} are higher in women, due to lower body weight, clinical significance unknown.
- **Race:** No data.
- **Other:** Higher drug exposure at lower body weight.

USES AND EFFICACY

Uses:

Effective treatment for **Type 2 diabetes mellitus**, in combination with metformin or metformin plus a sulfonylurea. In patients with a baseline HbA_{1c} 8.1-8.5%, liraglutide reduces HbA_{1c} from baseline by 0.6-1.5% with a daily dose of 0.6mg, by 0.8-1.5% with a 1.2mg dose, and by 1.1-1.5% with 1.8mg daily (by 2.4% if the baseline is above 10%). Effects on HbA_{1c} depend on the baseline level and dose. HbA_{1c} below 7% has been attained by approximately 50% of patients given 1.8mg daily over 26 weeks or more. Reduces fasting plasma glucose, postprandial glucose levels, and body weight.

Clinical course

Increased postprandial insulin secretion, reduced fasting plasma glucose, suppressed postprandial glucagon, and delay in gastric emptying begin with the first injection. A reduction in HbA_{1c} is detectable by week 8 reaching a maximum by week 12. Maximum reduction in fasting plasma glucose is attained by week 2.

Major clinical trials

Patients with an inadequate response to metformin or two oral drugs (LEAD-2) 2009: A randomized, double-blind, placebo- and active-controlled study in 1091 patients with T2DM (average HbA_{1c} 8.3-8.4, BMI 30-32 kg/m², disease duration 7-8 years, 65% previously treated with two drugs) compared treatment with metformin alone, metformin plus liraglutide, or metformin plus glimepiride. All patients were stabilized on metformin initially followed by a titration period on their assigned therapy. After a further 23-24 weeks, patients given metformin plus liraglutide 1.2 and 1.8mg, or metformin plus glimepiride 4mg, had lower HbA_{1c} levels (-1.0% vs. baseline) than those given metformin alone. HbA_{1c} reduction was greater (up to 1.3%) in patients who had previously been on monotherapy. Achievement by 32-45% of patients of the therapy goal of HbA_{1c} below 7% was dose-dependent, with 1.8mg liraglutide giving the best success; liraglutide 1.2mg and 1.8mg doses were not different from glimepiride 4mg. Fasting plasma glucose decreased by 1.1-1.8 mmol/L from baseline with no difference between the liraglutide and glimepiride groups. Postprandial glucose levels decreased in all treatment groups with no difference between liraglutide 1.2mg and 1.8mg compared with glimepiride. Patients given liraglutide lost 2-3 kg weight, highest with the 1.8mg dose, while those given glimepiride gained weight. All treatment groups had improvement in beta-cell function, as indicated by proinsulin-to-insulin ratios and HOMA-B. Gastrointestinal upset was common with liraglutide, occurring in 35-44% of patients vs. 17% with glimepiride or placebo, and led to withdrawal from the study in 5%. However, minor hypoglycemia was less frequent with liraglutide (3% vs. 17% with glimepiride). [Diabetes Care 2009;32:84-90.] **Study limitations:** The glimepiride dose of 4mg is not the

maximum dose, thus the potential effect of glimepiride may have been underestimated. The published article states that “The costs of publication of this article were defrayed in part by the payment of page charges”. *Study strengths:* A large, clinically relevant study.

Comparisons

Vs. sulfonylureas:

See Major Clinical Trials. In summary: Liraglutide 1.2-1.8mg is similar or better in efficacy to glimepiride, with less hypoglycemia and with weight loss instead of weight gain; however, GI upset including vomiting is common.

Vs. insulin:

A randomized, placebo-controlled study of patients with T2DM (baseline HbA1c 8.2 and BMI 30-31 kg/m² while treated with multiple oral glucose-lowering drugs) converted all patients to therapy with metformin plus glimepiride and then compared the addition of liraglutide 1.8mg with the open-label addition of insulin glargine at doses titrated to fasting plasma glucose. The addition of liraglutide to metformin plus glimepiride resulted in similar reductions in HbA1c as the addition of insulin glargine, but patients lost weight and had small reductions in systolic blood pressure while given liraglutide. Minor hypoglycemia was equally common with either treatment, and 5 events of major hypoglycemia were associated with liraglutide, attributed to the increased risk of hypoglycemia when liraglutide is combined with a sulfonylurea.

Vs. DPP-4 inhibitors:

Liraglutide is a subcutaneous injection that reduces weight, while DPP-4 inhibitors are oral drugs, weight neutral and generally well tolerated. Both have a low risk of hypoglycemia. Since DPP-4 serves many functions throughout the body, the effects of DPP-4 inhibitors are different from GLP-1 agonists such as liraglutide. DPP-4 inhibitors are significantly less effective for glycemic control than liraglutide.

Advantages

- Convenient once daily administration.
- Reduces postprandial plasma glucose.
- Very low risk of hypoglycemia (unless combined with a sulfonylurea drug).
- Benefit on HbA1c is comparable to, or better than, sulfonylureas or rosiglitazone.
- Mechanism of action differs from metformin, sulfonylureas, meglitinides, insulin and thiazolidinediones, making it useful in combination therapy.
- Has been safely combined with metformin, rosiglitazone, or a sulfonylurea (reduce dose of sulfonylurea to reduce hypoglycemia risk).
- Reduced need to self-monitor blood glucose, due to the low risk of hypoglycemia.
- Weight loss of 1-3 kg body weight.
- Reduces postprandial glucagon hypersecretion in T2DM, thereby reducing postprandial hyperglycemia.
- A cardiovascular benefit has been suggested, due to the lowering of systolic blood pressure and triglycerides, or other mechanisms; further research is needed.

Disadvantages

- Must be injected subcutaneously daily.
- Nausea, vomiting and diarrhea are common initially. Slow initial dose titration is recommended.
- Expensive.
- Contraindicated in patients with liver impairment or moderate to severe renal impairment.
- Does not decrease insulin resistance.
- As with all new drugs, there are unknowns. Long-term toxicity and long-term efficacy in this chronic, progressive disease are unknown. Effects may not be limited to glucose-lowering, since GLP-1 receptors are found throughout the body, in the CNS, peripheral nervous system, heart, lung, GI tract and kidney, as well as in islet alpha and beta cells. It is not known if it can be safely combined with insulin or DPP-4 inhibitors.
- Concerns exist over possible pancreatitis and thyroid tumors (see SIDE EFFECTS).
- No proven benefit on microvascular or macrovascular diabetic outcomes, the course of the disease, or on mortality.

Place in therapy

Liraglutide is an effective second-line treatment for patients with T2DM that avoids the hypoglycemic risk and weight gain associated with other diabetes drugs through a unique mechanism that addresses the deficiency in GLP-1. It will be most useful in patients who tolerate daily injections when hypoglycemia is a major concern, especially in those who require weight reduction. In patients not adequately controlled with 1-2 established drugs including metformin, the addition of liraglutide may be preferred to insulin. Careful attention to CONTRAINDICATIONS AND PRECAUTIONS is required. Although tested as monotherapy, liraglutide is not approved for this indication in Canada; there are safety concerns. Patients in the early stages of diabetes care may prefer and comply better with an oral agent.

Investigational/Unapproved Uses

- **Obesity:** Since liraglutide produces weight loss and decreased food intake in animals, and weight loss in humans, it has been investigated for the treatment of obesity in nondiabetic subjects. In a randomized, placebo-controlled trial, liraglutide doses of 1.2-3.0mg once daily progressively reduced weight in a dose-dependent manner by 2-4.4 kg more than placebo over 20 weeks. The mechanism is considered to be GLP-1-related suppression of appetite and delay of gastric emptying, and did not correlate with the common side effects of nausea and vomiting. Patients with severe comorbidities were excluded in this study, therefore safety in patients with underlying conditions is unknown.
- **Type 2 Diabetes mellitus: Monotherapy:** Patients with early T2DM (LEAD-3 Mono) 2009: A randomized, active-controlled, double-blind study of 746 patients with Type 2 diabetes mellitus (average baseline HbA1c 8.2%, BMI 32-33 kg/m²) compared once daily liraglutide with glimepiride 8mg. Patients were at an early stage of diabetes therapy, previously treated either with diet and exercise or with up to half of the maximum dose of a single oral hypoglycemic drug. After 52 weeks, HbA1c was reduced from baseline to a greater extent by liraglutide doses of 1.2mg (0.84%) and 1.8mg (1.14%) than by glimepiride (0.51%). Benefit on HbA1c was dose-related and greater in drug-naïve patients. More patients treated with liraglutide (43-51%) achieved HbA1c below 7% compared with glimepiride (28%). Liraglutide reduced fasting plasma glucose more than glimepiride; all treatments reduced postprandial glucose, with a greater effect from the 1.8mg liraglutide dose compared with glimepiride. Insulin resistance as measured by HOMA-IR was reduced with liraglutide only. Body weight increased with glimepiride but decreased with liraglutide. Minor hypoglycemic events were less common with liraglutide. Six patients given liraglutide withdrew from the study due to vomiting. [Lancet 2009;373:473-81.] *Study limitations:* No placebo group. Funded by the manufacturer of liraglutide. *Study strengths:* Large, long-term study; active comparator.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications

- Hypersensitivity.
- Type 1 diabetes mellitus (ineffective).
- Diabetic ketoacidosis (ineffective).
- Children under age 18 (no data).
- History of medullary thyroid carcinoma in the patient or the family or Multiple Endocrine Neoplasia Syndrome Type 2: Causes thyroid C-cell tumors in rodents at clinical doses; dose and duration dependent; risk in humans unknown; the benefit of monitoring with ultrasound or calcitonin levels as a marker for thyroid cancer is unclear. In humans there have been cases of thyroid C-cell hyperplasia.
- Pregnancy.
- Lactation.
- Hepatic impairment (limited data).
- Moderate or severe renal impairment (limited data).
- Inflammatory bowel disease or gastroparesis (nausea and diarrhea can occur; delays gastric emptying).

Precautions

- Patients with heart block, heart failure, recent MI or arrhythmias (tachycardia, PR interval prolongation, and heart block can occur).
- Thyroid disease or history of endocrine tumors (thyroid tumors in rodents; see SIDE EFFECTS).
- Elderly: Gastrointestinal adverse reactions are more common in patients over 70 years of age.

- Pancreatitis (rare cases have occurred; caution if there is a history of pancreatitis; monitor for symptoms; see SIDE EFFECTS).
- Blood glucose monitoring: Usually not required, unless combined with a sulfonylurea. Monitor HbA1c periodically.
- Patients with low body weight or losing weight (weight loss is common).
- Report unexpected or serious reactions to Canada Vigilance, the Canadian adverse drug reaction monitoring program.

PREGNANCY AND LACTATION

- **Pregnancy:** Teratogenic in animals at doses of 0.8 times the clinical exposure. Contraindicated.
- **Lactation:** Excreted in milk in animals. Contraindicated because of concerns of thyroid tumors reported in rodents.

SIDE EFFECTS

Cardiovascular:

- Tachycardia (increased heart rate by 2-8 bpm).
- PR interval prolongation (by 10msec).
- First degree AV block (2.6 vs. 1.4 with comparators per 1000 patient-years).
- Hypertension (2-3% of patients also given metformin vs. 2% with metformin alone).
- Decreased systolic blood pressure 2-8 mmHg with little change in diastolic blood pressure (possibly due to GLP-1-induced natriuresis).

CNS:

- Headache (5-12% combined with metformin vs. 7% with metformin alone).
- Dizziness (2-3% combined with metformin vs. 0.8% with metformin alone).
- Anxiety (0.4-1.7% combined with metformin vs. 0% with metformin alone).
- Depression (1.2-1.7% combined with metformin vs. 0% with metformin alone).

Dermatologic:

- Injection site reactions (pain, redness, swelling, itch).

Endocrine/Metabolic:

- Little increased risk of hypoglycemia unless combined with a sulfonylurea: Minor hypoglycemia in 27% of patients when a 1.8mg dose is combined with metformin plus glimepiride vs. 17% with metformin plus glimepiride; major hypoglycemia (0.06 vs. 0 events/year in these same groups).
- Decreased triglyceride levels (small reduction of 0.3mmol/L, in 15-20% of patients).
- Pancreatitis (rare but serious, 2.2 cases per 1000 subject-years vs. 0.6 with comparator). Necrotizing pancreatitis (1 fatal case).

Gastrointestinal:

- GI events in 41% of patients; dose-related (possibly due to delayed gastric emptying). Nausea, vomiting and diarrhea can lead to dehydration.
- Abdominal discomfort (1% combined with metformin vs. 0% with metformin alone).
- Abdominal pain (2-3% combined with metformin vs. 0% with metformin alone).
- Anorexia (2.5-6% and appears dose-related when combined with metformin vs. 0.8% with metformin alone).
- Appetite decreased (2-6% combined with metformin vs. 0% with metformin alone).
- Diarrhea (8-15% combined with metformin vs. 4% with metformin alone).
- Dyspepsia (2-7% combined with metformin vs. 0.8% with metformin alone).
- Gastritis (2.5-5% combined with metformin vs. 0.8% with metformin alone).
- Gastroesophageal reflux disease (0.4-1.7% combined with metformin vs. 0% with metformin alone).
- Nausea (up to 29% combined with comparators vs. 3-4% with comparator alone; mostly in the first 4 weeks of therapy).
- Satiety earlier than expected (0.4-1.3% combined with metformin vs. 0% with metformin alone).

- Vomiting (up to 17% vs. 4% with comparator).

Hematologic:

- Anemia (0.4-1.7% combined with metformin vs. 0% with metformin alone).

Hepatic:

- Hepatic steatosis (0.4-2.5% combined with metformin vs. 0% with metformin alone).

Renal:

- Decreased urine volume.

Respiratory:

- Bronchitis (2-4% combined with metformin vs. 0.8% with metformin alone).
- Sinusitis (0.4-1.7% combined with metformin vs. 0% with metformin alone).

Other:

- Antibodies to liraglutide (up to 13%, significance unknown).
- Cancer: Thyroid C-cell tumors in rodents. Increased serum calcitonin levels (in 1.9% of patients given 1.8mg/day vs. 0.8-1.1% with control medication). Papillary thyroid carcinoma (1.9 vs. 0.6 with control per 1000 subject-years; mainly microcarcinomas less than 1 cm). Malignant neoplasms (0.8% vs. 0.5% with active comparator). Benign thyroid neoplasms (1.1% vs. 1% with placebo).
- Diabetic retinopathy (1.7-2.1% combined with metformin vs. 0.8% with metformin alone).
- Pain in extremity (0-2.9% combined with metformin vs. 0.8% combined with metformin).
- Pyrexia (0.4-1.3% combined with metformin vs. 0% with metformin alone).
- Weight loss (1-3 kg, dose-related, due to loss of fat).

INTERACTIONS

Since liraglutide slightly slows gastric emptying, the absorption of oral drugs may be altered. In limited studies, delayed and lower peak levels have been found with acetaminophen, atorvastatin, lisinopril, oral contraceptives, and digoxin, but these effects are small and not considered clinically significant.

DRUG	EFFECT	MECHANISM	IMPORTANCE
Drugs that increase the heart rate*	Tachycardia	Additive	Caution
Drugs that increase the PR interval**	PR interval prolongation	Additive	Caution
Insulin	Unknown	Possibly additive effect	Avoid
Sulfonylureas	Increased risk of hypoglycemia	Unknown	Caution, consider lower sulfonylurea dose

*Drugs that increase the heart rate include: Beta agonists, sympathomimetics.

**Drugs that increase the PR interval include: Beta blockers, calcium channel blockers, digoxin, protease inhibitors.

PARENTERAL ADMINISTRATION

Subcutaneous injection only. Inject into the abdomen, thigh or upper arm.

DOSAGE

- The 1.8mg dose had a similar effect on HbA1c as the 1.2mg dose in some studies, and may increase GI toxicity.
- Exposure is lower at higher body weights. No dosage adjustment is generally required.

Adults:

Subcutaneous: Begin with a subtherapeutic dose to lessen gastric adverse reactions: 0.6mg once daily at any time of day for one week. Then increase the dose to 1.2mg once daily. After at least another week, the dose may be increased if required to 1.8mg once daily. If combined with a sulfonylurea drug, consider lowering the dose of the sulfonylurea to reduce the increased risk of hypoglycemia.

Elderly:

- No dosage change.

Hepatic impairment:

- Contraindicated.

Renal impairment:

- No dosage change in mild renal impairment. Contraindicated in moderate to severe renal impairment.

NURSING IMPLICATIONS

Educate the patient on the proper technique for subcutaneous injection. Encourage patients to use the product on a daily basis as prescribed. It can be injected at any time of day, but it will be easier to remember if it is injected around the same time each day.

Ensure patients are receiving a diabetic diet and an exercise program.

Observe patients (particularly elderly or debilitated individuals) for signs of drug-induced hypoglycemia (sweating, dizziness, pallor, tremor, tachycardia, confusion, fainting). However, this drug rarely causes hypoglycemia.

Record the presence and the estimated severity of symptoms of diabetes mellitus and associated hyperglycemia (polyuria, thirst, recurrent blurred vision, paresthesias, fatigue).

If diabetic treatment is being started or changed, construct a flow sheet to record the date, administration times and dosage of all hypoglycemic agents, including insulin, and results of blood and/or urine glucose tests.

PATIENT INSTRUCTIONS

Liraglutide (leer-A-gloo-tide) is used to treat type 2 diabetes.

Following your diet, exercise, and weight loss program is important for controlling glucose (sugar), and for the effectiveness of drug treatment.

Before taking this drug, be sure that your physician is aware if you have any of the following conditions: personal or family history of thyroid cancer; history of pancreatitis or pancreatic cancer; heart problems; liver problems; kidney problems; stomach problems including gastroparesis; current or planned pregnancy; breast feeding; any allergies or adverse reactions to medications; and of all medications that you are taking.

Take liraglutide exactly as prescribed by your physician. It must be taken regularly to be effective. It is injected subcutaneously once daily, at any time of the day. Taking it at the same time each day will help you to remember. Usual injection sites are the thighs, abdomen and upper arm.

If you miss a dose, take the dose the following day at the usual time. Do not take two doses to make up for a missed one.

Low blood sugar (hypoglycemia) is very uncommon with this medication. It is more common if you are also taking a sulfonylurea drug for diabetes. Symptoms of hypoglycemia are sweating, dizziness, lightheadedness, confusion, shakiness, drowsiness, marked hunger, fast heartbeat, trouble concentrating, headache that doesn't go away, or blurred vision. If any of these symptoms occur, take some sugar, fruit juice, a snack, or a meal. Contact your physician immediately.

Common side effects are nausea and diarrhea, which usually improve with time, and headache. If stomach problems occur, they can lead to fluid loss, therefore be sure to keep drinking fluids.

Other side effects are infrequent; but if any persistent or bothersome effects occur, especially vomiting, abdominal pain, back pain, dizziness, or palpitations, contact your physician.

In animals, this drug has caused thyroid tumors. Whether or not this can happen in humans is unknown. Tell your physician if you notice a lump in your neck, difficulty swallowing or breathing, or a hoarse voice.

If you have experienced an unexpected or serious reaction to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

Store this drug in the refrigerator, away from heat, light (keep the cap on) and moisture, and out of the reach of children. The pen in use can be stored for up to 30 days at room temperature or in the refrigerator. Dispose of needles and medicine safely – ask your pharmacist.

PRESENTATION:

Injection: 6mg/mL (3mL) in prefilled disposable pens.

References are available on request.

© 2011 BC Drug and Poison Information Centre