

Victoza® (Liraglutide): The Use of a GLP-1 Receptor Agonist in Type 2 Diabetes Mellitus

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Incretins are GI hormones that are released after meals to stimulate the pancreas in order to promote insulin secretion¹. The best known incretins are glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP)¹. GIP is not useful when it comes to type 2 Diabetes Mellitus (DM)¹. In the body, GLP-1 increases insulin secretion and decreases glucagon release, gastric emptying, and food intake. It also normalizes fasting and post prandial insulin secretion¹. The release of GLP-1 is directly related to the concentration of glucose in the bloodstream and thus GLP-1 is only released if glucose is present in the blood stream¹. The natural version of GLP-1 is broken down much too quickly in the body by dipeptidyl peptidase IV (DPP4) to be used as a therapeutic option for type 2 DM¹. Due to this fact, a synthetic version that would not be broken down as quickly was developed in July 2009 by Novo Nordisk called Victoza® (Liraglutide)². Liraglutide (6mg/ml) is nearly identical to the natural GLP-1 peptide with only one amino acid substitution and an added alpha glutamic acid spacer coupled to a fatty acid group¹. This change allows for albumin binding and an extended half life resulting in very convenient once daily dosing¹.

Mechanism of Action^{1,2,6,5,4}

GLP-1 receptors are expressed by beta cells which are found in tissues of the PNS, CNS, heart, vasculature, kidneys, lungs, and GI mucosa. Liraglutide acts as a long acting agonist at GLP-1 receptors which activates the cAMP-PKA pathway and several guanine exchange factors (GEFs). It also results in signals being initiated through PKC and PI3K and several ion channels being altered. The above actions result in increased biosynthesis and release of insulin in beta cells in a glucose dependent fashion. It also results in increased beta cell growth and replication, normalizes post prandial and fasting insulin secretion, slows gastric emptying, and thus decreases food intake. Liraglutide has also been shown to be beneficial in weight loss for type 2 diabetics with a loss of about 3kg being observed on average. Liraglutide has been shown to reduce A1C values by 0.8-1.4% and also have a low risk of hypoglycemic events.

Dosing^{4,6}

Liraglutide is available in a 0.6mg/ml pen formulation for Sub-Cutaneous administration at any time once daily. This convenient dosing is one of the major advantages of Liraglutide over other therapeutic options for type 2 diabetes. For the first week of therapy, 0.6 mg should be given OD. It is important to note that this dose will not provide effective glycemic control but is given this way in order to reduce GI side effects as the body becomes accustomed to the drug. The remainder of therapy should see 1.2mg OD as this level should provide sufficient glycemic control in most cases. Dosing may be increased to 1.8mg daily if insufficient glycemic control is observed.

Pharmacokinetics^{6,1}

Apparent Volume of Distribution: Sub Cutaneous-13 L Intravenous-0.07 L/kg.

Protein Binding: 98% Albumin Bound

Metabolism: Liraglutide is endogenously metabolized by DPP4 and endogenous endopeptidases at a much slower rate than that of natural GLP-1.

Bioavailability: Sub Cutaneous-55%

Half Life: 13 hours

tmax: 8-12 hours

Excretion: Found 6% and 5% as metabolites in urine and feces respectively.

Absorption: Liraglutide can reduce the rate and extent of absorption of orally administered drugs due to its effect on gastric emptying. This problem can be avoided by allowing at least 2 hours between administration of oral drugs and Liraglutide.

Clearance: Liraglutide is mainly cleared through metabolic pathways of plasma proteins.

Side Effects, Adverse Effects, Contraindications, Drug Interactions^{1,2,4,5,6}

The common side effects of Liraglutide are nausea, vomiting, and headache. Any GI disturbances are generally dose related and are reduced with continuing use. Other much less common side effects are diarrhea, constipation, hives, and dizziness. Also, Liraglutide has been associated with cases of pancreatitis although this is quite rare (<1%). There is also a link to thyroid tumour as tumours were found in mice with some being cancerous. In human studies 4 cases of thyroid tumours were found (1.3/1000) with a strong possibility that pre-existing disease had played a major factor. Patients should consult a health care professional if they experience persistent vomiting or diarrheah, abdominal pain, lumps or swelling in the neck, trouble swallowing, or unexplained hoarseness.

Liraglutide is contraindicated in those with a history or family history of Medullary Thyroid Carcinoma (MTC), patients with Multiple Endocrine Neoplasia Syndrome Type 2 (MEN2), Type 1 diabetics, and those with severe GI disease. Also, Liraglutide is not recommended for use in pregnancy as it was found to be teratogenic in animal studies. It is unclear as to the degree that Liraglutide is present in breast milk but therapy is currently not recommended while breast feeding. In clinical trials, Liraglutide was found to slightly increase the heart rate of participants. The significance of this result is not fully known as more studies need to be done, but currently caution is being urged in the use of Liraglutide in patients with pre-existing cardiac conditions. Liraglutide shows no difference in rate, extent, and effectiveness in all age groups although a slight increase in GI side effects may be experienced in those over seventy years of age. In addition, use in children is currently untested and thus not recommended. There is limited knowledge of the effect of Liraglutide in cases of renal or hepatic impairment, although, a structurally similar drug (Exenatide-BYETTA©) requires dosing changes for those who are renally impaired.

There are no severe drug interactions to be concerned about when using Liraglutide, but there are some worth mentioning. Oral and systemic corticosteroids, thiazide diuretics, luteinizing hormone releasing hormone analogs and somatropin may decrease the hypoglycemic effect of Liraglutide. Somatropin has the greatest effect and may warrant consideration for a therapeutic change. Also, pegvisomant may increase the hypoglycemic effect of liraglutide. In addition, when liraglutide is combined with sulfonylureas the hypoglycemic effect of the sulfonylurea will be augmented and a dosing change may be required. Liraglutide was also shown to decrease the area under the curve of digoxin, lisinopril, and

oral contraceptives by about 15%. Finally, caution should be exercised when consuming alcohol concomitantly with Liraglutide therapy.

Other information^{5,4,3,1,2,6}

Currently, Liraglutide is approved in Canada but is not on the Saskatchewan Formulary or covered by NIHB. Liraglutide may not be the greatest option for those who are not insured as it costs \$240/month, which is on the higher end for oral hypoglycemics. Liraglutide is an ideal choice for those type two diabetics who are having insufficient glycemic control in spite of proper diet, exercise, and previous oral hypoglycemic therapy. Liraglutide has been found to be useful in both adjunctive and monotherapy. Commonly seen combinations include concomitant use with metformin, sulfonylureas, or both. Also, combinations with metformin and thiazolidinediones have been successfully used. It is important to note that if Liraglutide is used with a sulfonylurea, the sulfonylurea dose should be decreased appropriately to avoid hypoglycemic events. Liraglutide is a good option for type 2 diabetics instead of a sulfonylurea or insulin in order to reduce the incidence of hypoglycemic events and promote weight loss. A similar drug that is currently on the market is Exenatide (BYETTA®). Exenatide is also a GLP-1 agonist but is slightly less effective, less tolerable, and has less convenient dosing. There are also concerns with renal function in Exenatide use. One advantage of Exenatide over Liraglutide is it is a less expensive option at \$140/month. Currently, much work is being put into advancing GLP-1 agonists' development. Research is currently being done to develop a GLP-1 agonist that can be administered at weekly intervals thus allowing for even greater convenience for type 2 diabetics and possibly greater disease control.

References:

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