WIKIPEDIA

Liraglutide

Liraglutide (NN2211) is a derivative of human incretin (metabolic hormone) glucagon-like peptide-1 (GLP-1) that is used as a long-acting glucagon-like peptide-1 receptor agonist, binding to the same receptors as does the endogenous metabolic hormone GLP-1 that stimulates insulin secretion. Marketed under the brand name **Victoza**, it is an injectable drug developed by Novo Nordisk for the treatment of type 2 diabetes. In 2015, Novo Nordisk began marketing a separate strength in the U.S. and E.U. under the brand name **Saxenda** as a treatment for adults who are obese or overweight with at least one weight-related comorbid condition.

The product was approved for treatment of type 2 diabetes by the European Medicines Agency (EMA) on July 3, 2009, and by the U.S. Food and Drug Administration (FDA) on January 25, 2010.[1][2][3] More recently, Liraglutide was approved by the FDA on December 23, 2014 and by the European Medicines Agency on January 23, 2015, for adults with a body mass index (BMI) of 30 or greater (obesity) or a BMI of 27 or greater (overweight) who have at least one weight-related condition.[4][5]

Contents

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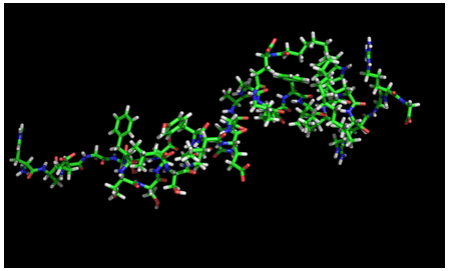

NMR structure of liraglutide. PDB entry 4apd (https://www.rcsb.org/structure/4apd)

Clinical data	
Trade names	Victoza, Saxenda
License data	EU EMA: by INN (http://www.ema.europa.eu/ema/index.jsp?curl=%2Fpages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keywordSearch=Submit

Medical uses

Liraglutide is a once-daily injectable derivative of the human incretin glucagon-like peptide-1 (GLP-1), for the treatment of type 2 diabetes or obesity.

Type 2 diabetes

Liraglutide improves control of blood glucose.[6] It reduces meal-related hyperglycemia (for 24 hours after administration) by increasing insulin secretion (only) when required by increasing glucose levels, delaying gastric emptying, and suppressing prandial glucagon secretion.[7][8] As of 2017 it is unclear if they affect a person's risk of death.[9]

In common to various degrees with other GLP-1 receptor agonists, liraglutide has advantages over more traditional therapies for type 2 diabetes:[2][7][10]

- It acts in a glucose-dependent manner, meaning it will stimulate insulin secretion only when blood glucose levels are higher than normal, preventing "overshoot". Consequently, it shows negligible risk of hypoglycemia.
- It has the potential for inhibiting apoptosis and stimulating regeneration of beta cells (seen in animal studies).
- It decreases appetite and inhibits body weight gain, as shown in a head-to-head study versus glimepiride.[11]
- It lowers blood triglyceride levels.[12]

Obesity

Liraglutide has been approved as an injectable adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients. The specified criteria are an initial body mass index (BMI) of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight), in the presence of at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia). In late 2014, data were reported from the SCALE™ Obesity and Prediabetes trial,[13] which is a randomised, double-blind, placebo-controlled, multinational trial in non-diabetic people with obesity and non-diabetic people who are overweight with comorbidities. In this phase 3a trial, there were 3,731 participants randomised to treatment with liraglutide 3 mg or placebo, both in combination with diet and exercise. Those who completed the 56-week trial achieved an average weight loss of 9.2%, to be compared with a 3.5% reduction in the placebo group.[14]

It is unknown if the weight loss will be permanent. Appetite suppression may be temporary and appetite might return even if one continues to use liraglutide after 56 weeks.

Adverse effects

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Pregnancy category	AU: B3 US: C (Risk not ruled out)
Routes of administration	subcutaneous
ATC code	A10BJ02 (WHO (https://www.whocc.no/atc_ddd_index/?code=A10BJ02))
Legal status	
Legal status	AU: S4 (Prescription only) CA: ℞-only UK: POM (Prescription only) US: ℞-only
Identifiers	
CAS Number	204656-20-2 (http://www.commonchemistry.org/ChemicalDetail.aspx?ref=204656-20-2)
PubChem CID	44147092 (https://pubchem.ncbi.nlm.ni

Thyroid cancer concerns

At exposures eight times greater than those used in humans, liraglutide caused a statistically significant increase in thyroid tumors in rats. The clinical relevance of these findings is unknown.[15] In clinical trials, the rate of thyroid tumors in patients treated with liraglutide was 1.3 per 1000 patient years (4 people) compared to 1.0 per 1000 patients (1 person) in comparison groups. The sole person in the comparator group and four of the five persons in the liraglutide group had serum markers (elevated calcitonin) suggestive of pre-existing disease at baseline.[15]

The FDA said serum calcitonin, a biomarker of medullary thyroid cancer, was slightly increased in liraglutide patients, but still within normal ranges, and it required ongoing monitoring for 15 years in a cancer registry.[16]

Pancreatitis concerns

In 2013, a group at Johns Hopkins reported an apparently statistically significant association between hospitalization for acute pancreatitis and prior treatment with GLP-1 derivatives (such as exenatide) and DPP-4 inhibitors (such as sitagliptin).[17] In response, the United States FDA and the European Medicines Agency conducted a review of all available data regarding the possible connection between incretin mimetics and pancreatitis or pancreatic cancer. In a joint 2014 letter to the New England Journal of Medicine, the agencies concluded that "A pooled analysis of data from 14,611 patients with type 2 diabetes from 25 clinical trials in the sitagliptin database provided no compelling evidence of an increased risk of pancreatitis or pancreatic cancer" and "Both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal."[18]

Pharmacodynamics

Liraglutide is an acylated glucagon-like peptide-1 (GLP-1) agonist, derived from human GLP-1-(7-37), a less common form of endogenous GLP-1.

Liraglutide leads to insulin release in pancreatic beta cells in the presence of elevated blood glucose. This insulin secretion subsides as glucose concentrations decrease and approach euglycemia (normal blood glucose level). It also decreases glucagon secretion in a glucose-dependent manner and delays gastric emptying. Unlike endogenous GLP-1, liraglutide is stable against metabolic degradation by peptidases, with a plasma half-life of 13 hours.[1][7]

	h.gov/compound/44147092)
IUPHAR/BPS	1133 (http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=1133)
DrugBank	DB06655 (https://www.drugbank.ca/drugs/DB06655)
ChemSpider	24571200 (http://www.chemspider.com/Chemical-Structure.24571200.html)
Chemical and physical data	
Formula	$C_{172}H_{265}N_{43}O_{51}$
Molar mass	3751.202 g/mol
3D model (JSmol)	Interactive image (https://chemapps.stolaf.edu/jmol/jmol.php?model=CCCCCCCCCCCCCCCC%28%3DO%29N%5BC%40%40H%5D%28CCC%28%3DO%29NCCCC%5BC%40H%5D%28NC%28%3DO%29%5BC%40H%5D%28C%29NC%28%3DO%29%5BC%40

Pharmacokinetics

Endogenous GLP-1 has a plasma half-life of 1.5–2 minutes due to degradation by the ubiquitous enzymes, dipeptidyl peptidase-4 (DPP4) and neutral endopeptidases (NEP). The half-life after intramuscular injection is approximately half an hour, so even administered this way, it has limited use as a therapeutic agent. The metabolically active forms of GLP-1 are the endogenous GLP-1-(7-36)NH_2 and the more rare GLP-1-(7-37). The prolonged action of liraglutide is achieved by attaching a fatty acid molecule at one position of the GLP-1-(7-37) molecule, enabling it to both self-associate and bind to albumin within the subcutaneous tissue and bloodstream. The active GLP-1 is then released from albumin at a slow, consistent rate. Albumin binding also results in slower degradation and reduced renal elimination compared to that of GLP-1-(7-37).[7]

Society and culture

Brand names

Liraglutide is marketed under the brand name Victoza in the U.S., U.K. UAE, Kuwait, India, Iran, Canada, Europe and Japan. It has been launched in Germany, Italy, Denmark, the Netherlands, the United Kingdom, Ireland, Sweden, Japan, Canada, the United States, Brazil, France, Malaysia and Singapore. Liraglutide is also known to be marketed as Saxenda in Australia, Canada and the U.S.

Marketing

Novo Nordisk stated that it plans to use 500 of its 3,000-strong sales force in the United States to promote Saxenda in 2015, because it is considered to have the potential for sales of $1 billion a year within 8–10 years of launch around the world. Analysts at Citi Research concur, assuming that the drug will reach less than 0.5 percent of the 107 million people in the United States classified as obese, and a daily price of $30 over 6 to 12 months' use. The company estimates that it has spent about $1 billion over ten years to take Saxenda from research to marketing.[4]

Controversy

In 2010, Novo Nordisk breached the ABPI's code of conduct by failing to provide information about side effects of Victoza, and by promoting Victoza prior to being granted market authorization.[19]

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In 2012, the non-profit consumer advocacy group Public Citizen petitioned the U.S. Food and Drug Administration (FDA) to immediately remove liraglutide from the market because they concluded that risks of thyroid cancer and pancreatitis outweigh any documented benefits.[20]

In 2017, Novo Nordisk agreed to pay $58.65 million to settle multiple whistleblower lawsuits alleging that the company had illegally marketed, promoted, and sold Victoza for off-label uses in violation of the Federal Food, Drug, and Cosmetic Act and the False Claims Act.[21] Novo Nordisk paid an additional $1.45 million to the states of California and Illinois to settle whistleblower cases alleging fraud against private commercial health insurers.[22]

Research

Phase I trials of an oral variant of Victoza (NN9924) started in 2010.[23]

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