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SAME SIZE ARTWORK
LEAFLET SIZE: 340 x 700 mm

For the use only of a registered medical practitioner or a hospital or a laboratory.

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LIRAGLUTIDE

Lirafit® लिराफिट

In a pre-filled pen of 3ml
For S.C. use

1. Generic Name

Liraglutide 6 mg/ml solution for injection (in prefilled pen) (rDNA Origin)
for subcutaneous use

2. Qualitative and quantitative composition

Each 1ml contains:
Liraglutide ..... 6 mg
Phenol I.P. (as preservative)..... 5.5 mg
Water for injection I.P. ..... q.s.

3. Dosage Form & strength

Solution for injection in pre-filled pen
Each pre-filled pen contains 18 mg liraglutide in 3 ml, solution that delivers doses of 3.0 mg, 1.2 mg or 1.8 mg.

4. Clinical particulars

4.1 Therapeutic indication

Liraglut® is used for the treatment of Type 2 diabetes mellitus.

4.2 Posology and method of administration

Dosing: a phase III clinical study in patients with Type-2 diabetes mellitus, Liraglut treatment was initiated with a starting dose of 0.6 mg daily for at least 1 week; After at least 1 week the dose was increased to 1.2 mg per day and thereafter the daily dose was maintained 1.2 mg or increased to 1.8 mg, depending on glycaemic control

Information provided below is based on clinical data.

To improve gastro-intestinal tolerability, the starting dose is 0.6 mg liraglutide daily. After at least one week, the dose should be increased to 1.2 mg. Some patients are expected to benefit from an increase in dose from 1.2 mg to 1.8 mg and based on clinical response, after at least one week, the dose can be increased to 1.8 mg to further improve glycaemic control. Daily doses higher than 1.8 mg are not recommended.

Liraglutide can be added to existing sulfonylurea or to a combination of metformin and sulfonylurea therapy or insulin. When liraglutide is added to sulfonylurea therapy or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see section 4.4). Self-monitoring of blood glucose is not needed in order to adjust the dose of the sulfonylurea when liraglutide is added. However, when initiating treatment with liraglutide in combination with a sulfonylurea or insulin, blood glucose self-monitoring may be necessary to adjust the dose of the sulfonylurea or the basal insulin.

Combination therapy with basal insulin is recommended in patients not achieving adequate glycaemic control with Liraglutide and metformin.

Special populations

Elderly patients (>65 years old)

No dose adjustment is required based on age. Therapeutic experience in patients ≥ 75 years of age is limited (see Pharmacokinetic properties).

Renal impairment

No dose adjustment is required for patients with mild, moderate or severe renal impairment. There is no therapeutic experience in patients with end stage renal disease and liraglutide is therefore not recommended for use in these patients. (See section 5.2 Pharmacokinetic properties).

Hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Liraglutide is not recommended for use in patients with severe hepatic impairment. (See section 5.3 Pharmacokinetic properties).

Paediatric population

The safety and efficacy of liraglutide as an adjunct to diet and exercise to improve glycaemic control in type 2 diabetes mellitus have not been established in paediatric patients 10 years of age and older. The risk of hypoglycaemia was higher in paediatric patients regardless of insulin and/or metformin use. The safety & effectiveness of liraglutide has not been established in paediatric patients less than 10 years of age (see Pharmacokinetic properties).

Method of Administration

Liraglutide must not be administered intravenous or intramuscularly.

Liraglutide is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that liraglutide is injected around the same time of the day, when the most convenient time of the day has been chosen. For further instructions on administration see section 6.5.

4.3 Contraindication

Hypersensitivity to the active substance or to any of the excipients.
Information provided is based on innovator data.

4.4 Special warnings and precautions for use

Liraglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Liraglutide is not a substitute for insulin.

There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV, and liraglutide is therefore not recommended for use in these patients.

There is limited experience in patients with inflammatory bowel disease and diabetic gastroparesis. Use of liraglutide is not recommended in these patients since it is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide should be discontinued. If acute pancreatitis is confirmed, liraglutide should not be restarted. Caution must be exercised in patients with history of pancreatitis (see section 4.8 and 5.1).

Thyroid disease

Liraglut is not recommended in patients with a personal or family history of Medullary Thyroid Cancer and Multiple Endocrine Neoplasia syndrome type 2.

Thyroid adverse events, such as goitre, have been reported in clinical trials and in particular in patients with preexisting thyroid disease. Liraglutide should not be used in such patients.

Hypoglycaemia

Patients receiving liraglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia (see section 4.8). The risk of hypoglycaemia can be lowered by a reduction in the dose of sulfonylurea or insulin.

Dehydration

Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported in patients treated with liraglutide. Patients treated with liraglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and advise precautions to avoid fluid depletion.
Information provided is based on innovator data.

4.5 Drugs interactions

In vitro, liraglutide has shown very low potential to be involved in pharmacokinetic interactions with other active substances related to cytochrome P450 and plasma protein binding.

The small delay of gastric emptying with liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption and therefore no dose adjustment is required. Few patients treated with liraglutide reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicinal products.

Warfarin and other coumarin derivatives

No interaction study has been performed. A clinically relevant interaction with active substances with poor solubility or with narrow therapeutic index such as warfarin cannot be excluded. Upon initiation of liraglutide treatment in patients on warfarin or other coumarin derivatives, more frequent monitoring of INR (International Normalised Ratio) is advised.

Paracetamol

Liraglutide did not change the overall exposure of paracetamol following a single dose of 1000 mg. Paracetamol was decreased by 31% and median Tmax was delayed up to 15 min. No dose adjustment is required when given with liraglutide.

Atorvastatin

Liraglutide did not change the overall exposure of atorvastatin to a clinically relevant degree following single dose administration of atorvastatin 40 mg. Therefore, no dose adjustment of atorvastatin is required when given with liraglutide. Atorvastatin Cmax was decreased by 38% and median tmax was delayed from 1 to 3 h with liraglutide.

Griseofulvine

Liraglutide did not change the overall exposure of griseofulvin following administration of a single dose of griseofulvin 500 mg. Griseofulvin Cmax increased by 37% while median tmax did not change. Dose adjustments of griseofulvin and other compounds with low solubility and high permeability are not required.

Digoxin

A single dose administration of digoxin 1 mg with liraglutide resulted in a reduction of digoxin AUC by 16%, decreased by 31%. Digoxin median tmax was delayed from 1 h to 3.5 h. No adjustment of digoxin dose is required based on these results.

Lisinopril

A single dose administration of 10 mg of 20 mg with liraglutide resulted in a reduction of lisinopril AUC by 15%, decreased by 27%. Lisinopril median tmax was delayed from 6 h to 8 h with liraglutide. No dose adjustment of lisinopril is required based on these results.

Insulin

No pharmacokinetic or pharmacodynamic interactions were observed between liraglutide and insulin detemir when administering a single dose of insulin detemir 0.5 U/kg with liraglutide 1.8 mg at steady state in patients with type 2 diabetes.
Information provided is based on innovator data.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Contraception: Liraglutide is a human glucagon-like peptide-1 (hGLP-1) analog, with a half-life of approximately 13 hours (see section 5.2). The treatment was initiated with a starting dose of 0.6 mg daily for at least 1 week. After at least 1 week the dose was increased to 1.2 mg per day and thereafter the daily dose was maintained at 1.2 mg or increased to 1.8 mg, depending on glycaemic control. The maintenance dose was reached after 2 weeks of treatment. The treatment was initiated with a starting dose of 0.6 mg daily for at least 1 week. After at least 1 week the dose was increased to 1.2 mg per day and thereafter the daily dose was maintained at 1.2 mg or increased to 1.8 mg, depending on glycaemic control. The duration of study treatment exposure and compliance was comparable in both the treatment groups, with a mean ± SD treatment duration of 168.7 ± 13.45 days and 164.28 ± 28.80 days and mean ± SD treatment compliance 99.47 ± 1.60% and 99.43 ± 1.89% in Liraglut and Victoza groups, respectively.

No SAEs were reported during the study. Death was reported in the study. A total of 146 AEs were reported by 57 subjects (44.5%) in the Liraglut group, and 77 AEs were reported by 35 subjects (42.0%) in the Victoza group.

A total of 132 Treatment-emergent adverse events (TEAEs) were reported by 165 (41.4%) subjects in the study. Among 135 TEAEs, 65 TEAEs were reported by 53 (41.4%) subjects and 70 TEAEs were reported by 53 (41.4%) subjects in the Liraglut group and Victoza group respectively.

Among the related TEAEs as judged by the investigators, 30 TEAEs were reported by 26 (20.3%) subjects in the Liraglut group and 40 TEAEs were reported by 35 (27.3%) subjects in the Victoza group. Majority of the reported TEAEs were mild in severity. A total of 8 hypoglycaemia events were reported by 6 (2.3%) subjects, including 2 events by 5 (3.9%) subjects in the Liraglut and a single event by 1 (0.8%) subject in the Victoza group. All the hypoglycaemic events were mild in severity and did not lead to discontinuation of study treatment. No injection site reactions were reported.

The most frequently reported (≥5%) TEAE was from the System Organ Class (SOCs) of Gastrointestinal Disorders and General Disorders and Administration Site Conditions. Overall in both the Liraglut and Victoza groups, the most frequently (≥2%) reported adverse event, in decreasing order of frequency were Gastrointestinal Disorders (39.0%), Nausea (5.1%), Asthenia (3.9%), Diarrhea (3.9%), Vomiting (2.7%), Pyrexia (2.2%), Headache (2.2%), Acid-peptic disease (2.3%) subjects overall. TEAEs reported during the study are summarized in Table 1.

Table 1: Summary of Treatment Emergent Adverse Events Reported in phase-3 comparative clinical study with Lirafit & Victoza:

System organ class Preferred term	Lirafit (N=329)	Total (N=256)
	Number of AEs (%; of patients)	Number of AEs (%; of patients)
Number of Patients with at least one TEAE	65 (41.4%)	135 (41.1%)
Cardiac Disorders	1 (0.8%)	1 (0.4%)
Ventricular Extrasystoles	1 (0.8%)	1 (0.4%)
Endocrine Disorders	0 (0%)	1 (0.4%)
Hypothyroidism	0 (0%)	1 (0.4%)
Eye Disorders	2 (1.6%)	2 (0.8%)
Diabetic Retinopathy	2 (1.6%)	2 (0.8%)
Gastrointestinal Disorders	55 (34.2%)	71 (24.0%)
Abdominal Pain	1 (0.8%)	2 (0.8%)
Acid Peptic Disease	3 (2.3%)	6 (2.3%)
Constipation	1 (0.8%)	1 (0.4%)
Diarrhoea	5 (4.7%)	9 (3.5%)
Dyspepsia	0 (0%)	1 (0.4%)
Gastritis	2 (1.6%)	3 (1.2%)
Gastrointestinal Disorder	10 (7.8%)	23 (9.0%)
Impaired Gastric Emptying	2 (1.6%)	2 (0.8%)
Nausea	5 (3.9%)	13 (5.1%)
Vomiting	5 (3.1%)	11 (2.7%)
General Disorders & Administration Site	12 (8.9%)	24 (9.0%)
Asthenia	3 (2.3%)	10 (3.9%)
Chest Pain	1 (0.8%)	1 (0.4%)
Chills	0 (0%)	2 (0.8%)
Fatigue	1 (0.8%)	2 (0.8%)
Fever	2 (1.6%)	2 (0.8%)
Pyrexia	5 (3.9%)	7 (2.7%)
Infections & Infestations	2 (1.6%)	7 (2.3%)
Gastroenteritis	1 (0.8%)	1 (0.4%)
Rhinitis	0 (0%)	1 (0.4%)
Upper Respiratory Tract Infection	0 (0%)	1 (0.4%)
Urinary Tract Infection	1 (0.8%)	4 (1.2%)
Injury, Poisoning & Procedural Complications	0 (0%)	1 (0.4%)
Ligament Sprain	0 (0%)	1 (0.4%)
Metabolism And Nutrition Disorders	8 (4.1%)	13 (4.3%)
Decreased Appetite	1 (0.8%)	4 (1.6%)
Hypoglycaemia	7 (3.9%)	8 (2.3%)
Increased Appetite	0 (0%)	1 (0.4%)
Musculoskeletal & Connective Tissue Disorders	0 (0%)	3 (1.2%)
Pain In Extremity	0 (0%)	3 (1.2%)
Nervous System Disorders	4 (3.1%)	9 (3.5%)
Burning Sensation	0 (0%)	2 (0.8%)
Headache	4 (3.1%)	7 (2.7%)
Skin & Subcutaneous Tissue Disorders	1 (0.8%)	3 (1.2%)
Hyperhidrosis	0 (0%)	1 (0.4%)
Miliaria	0 (0%)	1 (0.4%)
Pruritus	1 (0.8%)	1 (0.4%)

In the pharmacokinetic study carried out for Liraglutide (Bioavailability in 24 healthy human volunteers in a controlled setting with 0.6 mg single dose administered subcutaneously & separately at 0.6 mg multi dose administered subcutaneously for a period of 6 days and compared to Victoza, A total of 6 subjects only in the Victoza arm with 3 AEs of vomiting, 2 AEs of abdominal pain and 1 AE of hypoglycaemia were observed in post-study sample. The relationship of all the AEs was judged as possibly related and not severe. There was no Serious Adverse Event reported.

Information provided below is based on innovator data.

Summary of the safety profile

In five large long-term clinical phase 3a trials over 2,500 patients have received treatment with liraglutide alone or in combination with metformin, a sulfonylurea (with or without metformin) or metformin plus sulfonylurea.

The most frequently reported adverse reactions during clinical trials were gastrointestinal disorders: nausea and diarrhoea were very common, whereas vomiting, constipation, abdominal pain, and dyspepsia were common. At the beginning of the therapy, these gastrointestinal adverse reactions may occur frequently. These reactions usually diminish within a few days or weeks on continued treatment. Reactions at the injection site, nasopharyngitis were also common. Furthermore, hypoglycaemia was common, and very common when liraglutide is used in combination with a sulfonylurea. Severe hypoglycaemia has primarily been observed when combined with a sulfonylurea.

The adverse reactions reported with long-term combined trials of liraglutide are as follows. Frequencies are defined as: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Adverse reactions from long-term controlled phase 3a trials, the long-term cardiovascular outcome trial (LEADER) and spontaneous (post-marketing) reports

MedDRA system organ classes	Very Common	Common	Uncommon	Rare	Very rare
Infections and infestations		Nasopharyngitis Bronchitis			
Immune system disorders				Anaphylactic reactions	
Metabolism and nutrition disorders		Hypoglycaemia Anorexia Appetite decreased	Dehydration		
Nervous system disorders		Headache Dizziness			
Cardiac disorders		Increased heart rate			
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Dyspepsia Abdominal pain upper Constipation Gastritis Flatulence Abdominal distension Gastroesophageal reflux disease Abdominal discomfort Toothache	Intestinal obstruction	Pancreatitis (including necrotizing pancreatitis)	
Hepatobiliary disorders			Cholelithiasis Cholecystitis		
Skin and subcutaneous tissue disorder		Rash	Urticaria Pruritus		
Renal and urinary disorders				Renal impairment Renal failure acute	
General disorders and administration site conditions		Fatigue Injection site reactions	Malaise		
Investigations		Increased lipase Increased amylase			

Information provided below is based on innovator data.

Description of selected adverse reactions

In a clinical trial with liraglutide as monotherapy, rates of hypoglycaemia reported with liraglutide were lower than rates reported for patients treated with active comparator (glimepiride). The most frequently reported adverse reactions were gastrointestinal disorders, infections and infestations.

Hypoglycaemia

Most reactions of confirmed hypoglycaemia in clinical trials were minor. No episodes of severe hypoglycaemia were observed in the trial with liraglutide used as monotherapy. Severe hypoglycaemia may occur uncommonly and has primarily been observed when liraglutide is combined with a sulfonylurea (0.02 events/patient year). Very few episodes (0.001 events/patient year) were observed with administration of liraglutide in combination with oral antidiabetic other than sulfonylurea. The risk of hypoglycaemia is low with combined use of basal insulin and liraglutide (1.8 events per patient year, see section 5.1). In the LEADER trial, severe hypoglycaemic episodes were reported at a lower rate with liraglutide vs placebo (1.0 vs. 1.5 events per 100 patient years; estimated risk ratio 0.69 [0.51 to 0.93] (see section 5.2). For patients treated with premix insulin at baseline and at least for the following 26 weeks, the rate of severe hypoglycaemia was 2.2 events per 100 patient years.

Gastrointestinal adverse reactions

When combining liraglutide with metformin, 39.7% of patients reported at least one episode of nausea, and 12.6% of patients reported at least one episode of diarrhoea. When combining liraglutide with a sulfonylurea, 8.1% of patients reported at least one episode of nausea and 7.9% of patients reported at least one episode of diarrhoea. Most episodes were mild to moderate and occurred in a dose-dependent fashion. With continuation of treatment, the frequency and severity decreased in most patients who initially experienced nausea.

Patients ≥70 years may experience more gastrointestinal effects when treated with liraglutide.

Patients with mild and moderate renal impairment (creatinine clearance 60–90 ml/min and 30–59 ml/min, respectively) may experience more gastrointestinal effects when treated with liraglutide.

Cholelithiasis and cholecystitis

Few cases of cholelithiasis (0.4%) and cholecystitis (0.1%) have been reported during long-term, controlled phase 3b clinical trials with liraglutide. In the LEADER trial, the frequency of cholelithiasis and cholecystitis was 1.2% and 1.1% for liraglutide and 1.1% and 0.7% for placebo, respectively (see section 5.2).

Withdrawal

The incidence of withdrawal due to adverse reactions was 7.8% for liraglutide-treated patients and 3.4% for comparator treated patients in the long-term controlled trials (28 weeks or longer). The most frequent adverse reactions leading to withdrawal for liraglutide-treated patients were nausea (2.8% of patients) and vomiting (1.5%).

Injection site reactions

Injection site reactions have been reported in approximately 2% of patients receiving liraglutide in long-term (28 weeks or longer) controlled trials. These reactions have usually been mild.

Pancreatitis

Few cases of acute pancreatitis (<0.2%) have been reported during long-term, controlled phase 3 clinical trials with liraglutide. Pancreatitis was also reported from marketed use. In the LEADER trial, the frequency of acute pancreatitis confirmed by adjudication was 0.4% for liraglutide and 0.5% for placebo, respectively (see sections 4.4 and 5.2).

Allergic reactions

Allergic reactions including urticaria, rash and pruritus have been reported from marketed use of liraglutide.

Few cases of anaphylactic reactions and other antidiabetic symptoms such as hypoglycaemia, palpitations, dyspnoea and oedema have been reported with marketed use of liraglutide. Few cases (0.09%) of angioneurotic have been reported during all long-term clinical trials with liraglutide.

Immunogenicity of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risks balance of the medicinal product.

Information provided is based on innovator data.

4.9 Overdose

From clinical trials and marketed use, overdoses have been reported of up to 40 times (72 mg) the recommended maintenance dose. Generally, the patients reported severe nausea, vomiting and diarrhoea. None of the patients reported severe hypoglycaemia. All patients recovered without sequelae.

Upon overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

5. Pharmacological properties

5.1 Mechanism of action

Liraglutide is a GLP-1 analogue with 97% sequence homology to human GLP-1 that binds to and activates the GLP-1 receptor. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion. The receptor is a seven transmembrane receptor, coupled to adenylate cyclase, and has a cytoplasmic membrane protein in tamous outside the cell. The receptor is expressed in a number of tissues including the beta cells of the pancreas, the kidneys, the central nervous system, the cardiovascular system, the gastrointestinal tract and the immune system. Native GLP-1 has a plasma half-life of less than 2 minutes after intravenous administration, the pharmacological activity of liraglutide is based on three mechanisms: self-association, which results in slow absorption; binding to albumin; and hydrolysis enzymatic stability towards dipeptidyl peptidase (DPP) enzymes and renal elimination, resulting in a long plasma half-life.

Liraglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cyclic adenosine monophosphate (cAMP). Liraglutide stimulates insulin secretion in a glucose-dependent manner. Consequently, in hyperglycaemia, the insulin secretion is a glucose-dependent response. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, during hypoglycaemia liraglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose lowering also involves a similar delay in gastric emptying. Liraglutide reduces body weight and body fat mass through mechanisms not fully elucidated but including reduced hunger and lowered energy intake.

5.2 Pharmacodynamic properties

Liraglutide has 24-hour duration of action and improves glycaemic control by lowering fasting and postprandial blood glucose in patients with type 2 diabetes mellitus.

Clinical efficacy and Safety

In the Phase 3 clinical study done with Lirafit to compare against Victoza involving 256 patients with Type-2 diabetes mellitus and on oral antidiabetic medication, the change from baseline (Least square mean +/- Standard Error) in HbA1c was -1.09 (-0.13%) (95% CI: -1.4 ; -0.78) for Lirafit after 26 weeks of treatment compared to reduction of -1.34 (-0.14%) (95% CI: -1.56 ; -0.72) for Victoza group. Non-inferiority could not be non-inferior to Victoza as the upper limit of 95% CI for the difference in mean HbA1c change from baseline (Week 26-Baseline) between the treatment groups (Lirafit - Victoza) was 0.20 (p-value = 0.021).

The proportions of subjects who achieved reduction of HbA1c by ≥ 0.5% from the 24 week treatment was comparable between the two groups, with 68.3% patients treated with Lirafit and 71% patients treated with Victoza (p-value = 0.06) and reduction of HbA1c by ≥ 1% achieved in 54.8% and 64% patients treated with Lirafit & Victoza respectively (p-value = 0.06). The reduction (least square mean) in weight was 2.4 kg (-2.6%) in Lirafit and 2.4 kg (-2.8%) in Victoza treated patients (95% CI: -2.4 ; -0.4 ; -4.3) for Lirafit and reduction of 1.6 kg (-1.8%) (95% CI: -2.4 ; -0.8 ; -2.9) for Victoza group (p-value = 0.05). For Post prandial blood sugar, the reduction was 29.7 mg/dl (-16% CI: -21.25 ; -16.69) (95% CI: -38.41 ; -15.34) respectively. The reduction (Least mean square) in body weight from baseline was 1.87 kg (2% CI: -3.05 ; -0.64) in Lirafit and 1.5 kg (-1.8%) (95% CI: -2.41 ; -0.51) after 24 weeks of treatment and comparable with Victoza (p-value = 0.05).

There was reduction also seen in systolic blood pressure in the Lirafit & Victoza groups an average of -3.49 ± 10.4 mmHg and -2.60 ± 8.2 mmHg respectively.

Lirafit was well tolerated and its safety was comparable to Victoza in adults with type 2 diabetes mellitus. For adverse events observed in the clinical trial, see section 4.8.

Information provided is based on innovator data.

Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.

Five double-blind, randomised, controlled clinical phase 3b trials were conducted to evaluate the efficacy and safety of liraglutide on glycaemic control (Table 2). Treatment with liraglutide produced clinically and statistically significant improvements in glycaemic control and reduced bodyweight when added to other antidiabetic medicinal products.

These trials included 1,970 exposed patients with type 2 diabetes mellitus (2,501 patients treated with liraglutide), 53.7% men and 46.3% women, 797 patients (508 treated with liraglutide) were ≥65 years of age and 113 patients were ≥75 years of age. The mean age was 55 years.

Additional trials were conducted with liraglutide that included 1,901 patients in four additional open-label, controlled clinical trials (including 464, 658, 323 and 177 patients on trial) and one double-blind, randomised, controlled clinical trial in patients with type 2 diabetes mellitus and moderate renal impairment (279 patients).

A large cardiovascular outcomes trial (the LEADER Trial) was also conducted with liraglutide in 9,340 patients with type 2 diabetes mellitus at high cardiovascular risk.

Glycaemic control

Monotherapy

Liraglutide monotherapy for 52 weeks resulted in statistically significant and sustained reductions in HbA1c compared with placebo (-0.84% for 1.2 mg, -1.14% for 1.8 mg vs -0.01% for comparator) in patients previously treated with either diet and exercise or OAD monotherapy, at no more than half-maximal dose (Table 3).

Combination with oral antidiabetics

Liraglutide in combination therapy, for 26 weeks, with metformin, glimepiride or metformin and rosiglitazone resulted in statistically significant (p-0.0031) and sustained reductions in HbA1c compared with patients receiving placebo (Table 3).

Table 3: Liraglutide clinical phase 3a trials in monotherapy (52 weeks) and in combination with oral antidiabetics (26 weeks)

	N	Mean baseline HbA1c (%)	Mean HbA1c change from baseline (%)	Patients (%) achieving HbA1c<7%	Mean baseline weight (kg)	Mean weight change from baseline (kg)
Monotherapy						
Liraglutide 1.2 mg	251	8.18	- 0.84*	42.8*, 58.3*	92.1	- 2.35**
Liraglutide 1.8 mg	246	8.19	- 1.14**	50.9*, 62.0*	92.5	- 2.45**
Glimepiride 8 mg/day	248	8.23	0.51	27.8*, 36.8*	90.3	1.12
Add-on to metformin (7,000 mg/day)						
Liraglutide 1.2 mg	240	8.3	- 0.97*	35.3*, 52.8*	88.5	- 2.98**
Liraglutide 1.8 mg	242	8.4	- 1.05*	42.4*, 66.3*	88.3	- 2.79**
Glimepiride 4 mg/day	121	8.4	0.09	10.8*, 29.3*	91.9	- 1.51
Placebo	242	8.4	0.36	26.2*, 38.0*	89.9	0.90
Add on to glimepiride 4 mg/day						
Liraglutide 1.2 mg	228	8.5	- 1.06**	34.5*, 57.4*	80.9	0.32**
Liraglutide 1.8 mg	234	8.5	- 1.03**	41.6*, 61.9*	83.3	- 0.23**
Placebo	114	8.4	0.23	7.5*, 11.8*	81.9	- 0.16
Rosiglitazone 4 mg/day	231	8.4	- 0.44	21.9*, 28.1*	80.6	2.11
Add-on to metformin (7,000 mg/day) + rosiglitazone (4 mg twice daily)						
Liraglutide 1.2 mg	177	8.48	- 1.48	57.5*	95.3	- 1.92
Liraglutide 1.8 mg	178	8.56	- 1.48	53.7*	94.9	- 2.92
Placebo	175	8.42	- 0.54	21.2*	98.5	0.60
Add-on to metformin (2,000 mg/day) + glimepiride 4 mg/day						
Liraglutide 1.8 mg	230	8.3	- 1.33*	53.1*	85.6	- 1.81**
Placebo	114	8.3	0.24	15.3*	85.4	0.42
Insulin glargine#	232	8.1	- 1.39	45.8*	85.2	1.62

*Superiority (p-0.01) vs active comparator; **Superiority (p-0.0001) vs active comparator; †Non-inferiority (p<0.0001) vs active comparator
all patients; ‡previous OAD monotherapy; §previous diet treated patients
#the dosing of insulin glargine was open-labelled and was applied according to Guideline for titration of insulin glargine. Titration of the insulin glargine dose was managed by the patient after instruction by the investigator
Guideline for titration of insulin glargine

Self-measured PPG	increase in insulin glargine dose (IU)
>5.5 mmol/l (>100 mg/dl) Target	No adjustment
>5.5 and <6.7 mmol/l (>100 and <120 mg/dl)	0-2 IU*
≥6.7 mmol/l (≥120 mg/dl)	2-4 IU*

*adjustment to the next whole unit dose recommendation by the investigator of the previous visit, for example dose regimen whether the patient has experienced hypoglycaemia

Combination with insulin

In a 104-week clinical trial, 57% of patients with type 2 diabetes treated with insulin glargine in combination with metformin achieved a target HbA1c <7% and the remaining patients continued in a 26-week open-label extension phase where they were allowed to add liraglutide to a single daily insulin injection. In the insulin glargine + liraglutide arm, the insulin dose was reduced by 26% in order to minimise the risk of hypoglycaemia. Addition of liraglutide resulted in a statistically significantly greater reduction of HbA1c (-0.73% for liraglutide vs -0.40% for comparator) and body weight (-3.03 vs -0.73 kg). The rate of hypoglycaemia (severe or confirmed episodes per patient year of exposure) was statistically significantly lower with adding a single dose of insulin detemir (1.41 vs 6.15, ratio: 0.19; 95% CI: 0.08 to 0.31).

In a cross-over study, the administration of insulin detemir 0 liraglutide 1.8 mg and metformin in patients not achieving glycaemic targets on liraglutide and metformin alone resulted in a HbA1c decrease from baseline of 0.84%, compared to 0.20% in the liraglutide 1.8 mg and metformin control group. Weight loss was sustained. There was a small increase in the rate of minor hypoglycaemic episodes (2.1 vs 1.5 episodes per patient year).

In the LEADER trial, (see section Cardiovascular evaluation), 673 patients were on premix insulin (with or without OAD(s)) at baseline and at least for the following 26 weeks. The mean HbA1c at baseline was 8.7% for liraglutide and placebo. At week 26, the estimated mean change in HbA1c was -1.4% and -0.5% for liraglutide and placebo, respectively, with an estimated treatment difference of -0.9 (-0.93; -0.78%) CI. The safety profile of liraglutide in combination with premix insulin was overall comparable to that observed for placebo in combination with premix insulin (see section 4.8).

Use in patients with renal impairment

In a double-blind trial comparing the efficacy and safety of liraglutide 1.8 mg versus placebo as add-on to insulin and/or OAD in patients with type 2 diabetes and moderate renal impairment, liraglutide was superior to placebo in reducing HbA1c after treatment for 26 weeks (-0.38% vs -0.26%). Liraglutide was generally more patients achieved HbA1c below 7% with liraglutide compared with placebo (52.8% vs 18.5%). In both groups a decrease in body weight was seen: -2.4 kg with liraglutide vs -1.09 kg with placebo. There was a comparable risk of hypoglycaemic episodes between the two treatment groups. The safety profile of liraglutide was generally similar to that observed in other studies with liraglutide.

Proportion of patients achieving reductions in HbA1c

Liraglutide alone resulted in a statistically significant greater proportion of patients achieving HbA1c ≤6.5% at 52 weeks compared with patients receiving glimepiride (37.8% for 1.8 mg and 28.0% for 1.2 mg) and comparable to the proportion of patients treated with placebo.

Liraglutide in combination with metformin, glimepiride, or metformin and rosiglitazone resulted in a statistically significant greater proportion of patients achieving an HbA1c ≤6.5% at 26 weeks compared with patients receiving these agent alone.

Fasting plasma glucose

Treatment with liraglutide alone and in combination with one or two oral antidiabetic drugs resulted in a reduction in fasting plasma glucose of 13-4.3 mg/dl (0.72-2.42 mmol/l). This reduction was observed within the first few weeks of treatment.

Postprandial glucose

Liraglutide reduced postprandial glucose across all three daily meals by 31 –49 mg/dl (1.68–2.71 mmol/l).

Beta-cell function

Clinical trials with liraglutide indicate improved beta-cell function based on measures such as the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio. Improved first and second phase insulin secretion in response to a glucose challenge was observed in a dedicated study in patients with type 2 diabetes mellitus.

Body weight

Liraglutide alone and in combination with metformin, metformin and glimepiride or metformin and rosiglitazone or SU(2) with or without metformin was associated with sustained weight reduction over the duration of trials in a range from 0.86 kg to 2.62 kg compared to placebo.

Larger weight reduction was observed with increasing body mass index (BMI) at baseline.

Cardiovascular evaluation

Blood pressure: Over the duration of the trials, liraglutide decreased the systolic blood pressure on average of 2.3 to 5.7 mmHg from baseline, and compared to active comparator, the decrease was 1.6 to 4.9 mmHg.

Post-hoc analysis of serious major adverse cardiovascular events (cardiovascular death, myocardial infarction, stroke) from all intermediate and long-term phase 3 and 3b trials (ranging from 26 and up to 160 weeks duration) including 8,667 patients (5,681 exposed to liraglutide), showed no increase in cardiovascular risk (incidence rate of 0.35 (95% CI: 0.31, 1.63) for liraglutide versus all comparators.

The Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results (LEADER) trial, was a multicentre, placebo-controlled, double-blind clinical trial. 9,340 patients were randomly allocated to either liraglutide (4,668) or placebo (4,672), both in addition to standards of care for HbA1c and cardiovascular (CV) risk factors. The duration of observation was minimum 3.5 years and up to a maximum of 5.5 years. The study population included patients with years (n=4,739) aged ≥ 50 years with at least one of the following: CV disease, chronic kidney disease (CKD) stage 3 or higher, chronic congestive heart failure (CHF) or chronic heart failure (CHF) with left ventricular hypertrophy (LVH), or chronic heart failure (CHF) with left ventricular hypertrophy (LVH) and moderate renal impairment (n=2,591), moderate (n=1,204) or severe (n=224) renal impairment.

Liraglutide significantly reduced the occurrence of major adverse cardiovascular events (MACE). The estimated hazard ratio (95% CI) for time to first MACE was 0.87 (0.78, 0.97). The estimated hazard ratio of time to all-cause death for liraglutide versus placebo was 0.85 (0.74, 0.97). Liraglutide also significantly reduced the risk of expanded MACE (primary MACE, unstable angina patients leading to hospitalisation, coronary revascularisation, or hospitalisation due to heart failure) and other secondary endpoints.

Immunogenicity

In the phase 3 comparator clinical trials with Lirafit and Victoza, the immunogenicity was checked with a validated assay and after 24 weeks of treatment, anti-liraglutide antibodies were found in only 3.8% of the patients in Lirafit and 3.1% in the Victoza group for blood samples drawn at week 26. Further the antibody titer levels in all the confirmed positive samples were found to be low, implying low immunogenicity levels with both treatment groups. Further increase in the titer levels were observed in the patients who had reached the HbA1c target.

Information provided is based on innovator data.

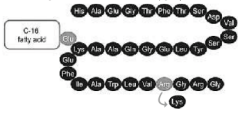
Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop anti-liraglutide antibodies following treatment with liraglutide. On average, 8.8% of patients developed antibodies. Antibody formation has not been associated with reduced efficacy of liraglutide.

5.3 Pharmacokinetic properties

The pharmacokinetics of Lirafit was assessed in 24 healthy human volunteers in a controlled setting with 0.6 mg single dose administered subcutaneously & separately as 3.6 mg multi dose administered subcutaneously for a period of 6 days.

In the single-dose study, the geometric mean

The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is:



Liraglutide is a clear, colorless or almost colorless solution, pH 7.2 to 7.5. Each 1 mL of Liraglutide solution contains 6 mg of Liraglutide and the following inactive ingredients: Disodium hydrogen Phosphate Dihydrate, 1.42 mg; Glycerol 16 mg; Phenol, 5.5 mg; Sodium hydroxide, Hydrochloric Acid and Water for Injection. Each pre-filled pen contains a 3 ml, solution of Liraglutide equivalent to 18 mg Liraglutide (free-base, Anhydrous).

4. Pharmaceutical particulars

8.1 Incompatibilities

Substances added to Liraglutide may cause degradation of liraglutide. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

8.2 Shelf-Life

The shelf life of the product is 30 months when stored at 2°C to 8°C

After first use: 1 month.

8.3 Packaging information

Cartridge (type 1 glass) with a plunger (bromobutyl) and a combi seal (bromobutyl) contained in a pre-filled multi dose disposable pen.

Each pen contains 3 ml solution, delivering 30 doses of 0.6 mg, 15 doses of 1.2 mg or 10 doses of 1.8 mg.

Pack size of 1 pre-filled pen.

8.4 Storage and handling instructions

- Store in a refrigerator between 2°C to 8°C. Do not freeze or store in the freezer compartment. After first use: store in a refrigerator between 2°C to 8°C. Do not freeze. Keep the pen cap on in order to protect from light. Keep out of reach of children.
- Liraglut should not be used if it does not appear clear and colourless or almost colorless.
- Liraglut should not be used if it has been frozen.
- Liraglut can be administered with pen needles up to a length of 8 mm and as thin as 32G. The pen is designed to be used with BD/Ambecta Ultrafine, NovoFine or NovoTwist or equivalent disposable pen needles.
- Needles are not included.
- The patient should be advised to discard the injection needle in accordance with local requirements after each injection and store the pen without an injection needle attached. This prevents contamination, infection and leakage. It also ensures that the dosing is accurate.

9. Patient Counselling Information

Risk of Thyroid C-cell Tumors

In preclinical studies of liraglutide in mice and rats, benign and malignant thyroid C-cell tumors have been observed. The human relevance of this finding has not been determined. Patients should be counselled to report symptoms of thyroid tumours (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnoea) to their physician.

Dehydration and Renal Failure

The gastrointestinal adverse reactions to Liraglutide Biosimilar includes potential risk of dehydration and to advise patients to take precautions to avoid fluid depletion. Potential risk for worsening renal function should be inferred to patients, which in some cases may require dialysis.

Pancreatitis

Liraglutide has potential risk for pancreatitis. Counsel patients on possible persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting. Instruct patients to discontinue Liraglut promptly and contact their physician if persistent severe abdominal pain occurs.

Acute Gallbladder Disease

Liraglutide has potential risk for cholelithiasis or cholecystitis. Patients should be instructed to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up.

Never Share a Liraglutide Biosimilar Pen Between Patients

Patients should be advised never to share Liraglut pen with another person as there is a risk for transmission of blood-borne pathogens, even if the needle is changed.

Hypersensitivity Reactions

Serious hypersensitivity reactions have been reported during postmarketing use of liraglutide. Counsel patients on the symptoms of hypersensitivity reactions and to discontinue taking Liraglut and seek medical advice promptly if such symptoms occur.

Jaundice and Hepatitis

Jaundice and hepatitis have been reported during post-marketing use of liraglutide. Advise patients to contact their physician if they develop jaundice.

Instructions

Counsel patients that the most common side effects of Liraglut are headache, nausea and diarrhoea.

The most common side effects is nausea when first starting Liraglut, but decreases over time in the majority of patients and does not typically require discontinuation of Liraglut.

If the patient misses a dose, instruct patients not to take any extra dose of Liraglut to make up for it. In case of missed dose, the once-daily regimen should be resumed as prescribed with the next scheduled dose. If the gap from the last dose is more than 3 days, advise the patient to reinitiate Liraglut at 0.6 mg to mitigate any gastrointestinal symptoms associated with reinitiation of treatment. Liraglut should be titrated at the discretion of the prescribing physician.

Adverse Reactions Refer part 4.8

Reporting of side effects or suspected adverse reaction: If you experience any side effects, talk to your doctor or pharmacist. You can also report side effects directly by calling on toll free no. 18002662255 or mail at globalcustomerservice@glenmarkpharma.com. By reporting side effects, you can help provide more information on the safety of this product.

Drug interactions Refer part 4.5

Dosage Refer part 3

Storage Refer part 8.4

Risk Factors Refer part 4.4

Self-monitoring information NA

Information on when to contact a health care provider or seek emergency help: Patients are advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

Contraindications Refer part 4.3

10. Details of manufacturer

Leviter Biotech LLP

AL L-7, MIDC Industrial Area,

Taloja, Raigad, Maharashtra - 410 208.

11. Details of permission or licence number with date

Refer Carton

12. Date of revision: October 2023

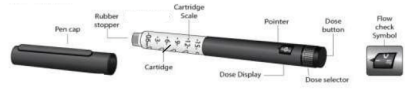
Instructions for using the Lirafit® pen

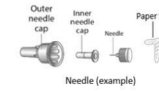
(Pen User Manual)

Please read these instructions carefully before using your pen

The pen contains 18 mg of Liraglutide & capable of delivering doses of 0.6 mg, 1.2 mg and 1.8 mg. The pen is designed to be used with disposable pen needles such as BD/embecta Ultrafine, NovoFine or NovoTwist up to a length of 6 mm and as thin as 32G (0.25 / 0.23 mm).

Lirafit® Pen



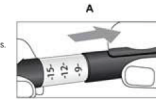


Needle (example)

Step I. Prepare Your Pen

- Wash hands with soap and water before use. Take a new pen out of the refrigerator.
- Pull off pen cap (image A).
- Check the product in the cartridge: The liquid should be clear, colorless and free of particles.

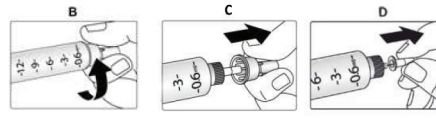
A



Step II. Attach the Needle

- Pull off the paper tab from a new disposable needle.
- Screw the needle straight and tightly on to your pen (image B).
- Pull off outer needle cap. Do not throw away and keep it for later (image C).
- Pull off the inner needle cap and dispose it. A small drop of liquid may appear. This is normal (image D).

B C D



Step III. With each new pen, check the flow

Priming of Pen:

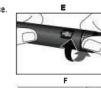
This step is done only ONCE for each new pen and is ONLY required the first time you use a new pen. For every subsequent use, proceed to Step IV

Note:

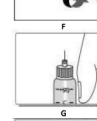
1. **You will hear a "click" every time you turn the dose selector. Do not use these clicks to select your dose.**
2. The flow check symbol does not administer the dose as prescribed by your healthcare provider.

- Turn dose selector until flow check symbol (--) lines up with pointer (image E).
- Hold pen with needle pointing up and tap the cartridge gently with your finger a few times to bring any air bubbles to the top of the cartridge (image F).
- Keep needle pointing up, press the dosing button until 0 mg lines up with the pointer.
- A drop of Liraglutide should appear at the needle tip. If no drop appears, repeat the process in Step III (images E – G) up to four times until a drop appears at the needle tip.
- Do not use the pen if a drop of Liraglutide still does not appear. This indicates the pen is defective and you must use a new one.

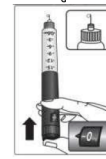
E



F



G



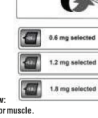
Step IV: Select your dose

Always check that the pointer lines up with 0 mg

- Turn the dose selector until the required dose lines up with the pointer mark (0.6 mg, 1.2 mg or 1.8 mg). (image H)
- If you selected a wrong dose by mistake, simply change it by turning the dose selector backwards or forwards until the correct dose lines up with the pointer.
- Do not try to select other doses than 0.6 mg 1.2 mg or 1.8 mg. The numbers in the display must precisely line up with the pointer to ensure that you get the correct dose.
- Be careful not to press the dose button when turning the dose selector backwards as Liraglutide may come out
- If your dose selector stops before your needed dose lines up with the pointer, or there is not enough Liraglutide left for full dose. Then you can do either of the following:

1. Split your dose into two injections:
   a) Turn the dose selector in either direction until 0.6 mg or 1.2 mg lines up with the pointer, inject the dose. Then prepare a new pen for injection and inject the remaining number of mg to c o m p l e t e your dose.
   b) You may only split your dose between your current pen and a new pen if trained or advised by your healthcare professional. Use a calculator to plan the doses. If you split the dose wrong, you may inject too much or too little Liraglutide.
2. Inject the full dose with new pen:
   If the dose selector stops before 0.6mg lines up with the pointer, prepare a new pen and inject the full dose with the new pen.

H

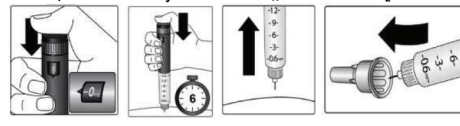


Step V. Injecting the Dose

Use the injection technique shown to you by your healthcare provider. Then follow the instructions below:

- **Insert needle into your skin in the abdomen, thigh or upper arm. Do not inject the product into a vein or muscle.**
- Gently press down the dose button to inject until 0 mg lines up with the pointer (image I).
- Be careful not to touch the display with your other fingers or press the dose selector sideways when you inject. This is because it may block the injection.
- Keep the dose button pressed down and leave the needle under the skin for at least 6 seconds (image J). This is to make sure that you get your full dose.
- Pull out the needle (image K). You may see a drop of Liraglutide at the needle tip. This is normal and it does not affect your dose.
- Change (rotate) your injection sites within the area you choose for each dose. Do not use the same injection site for each injection.

I J K L



- After each use, carefully guide the needle tip into the outer needle cap without touching the needle or the outer needle cap (image L). When the needle is covered, carefully push the outer needle cap completely on. Then unscrew the needle from the pen.
- Safely discard the needle.
- Re-attach the cap to the pen.
- **Store the pen in 2°C to 8°C (36°F to 46°F) without an injection needle attached until next dose.**
- When the pen is empty, carefully dispose of it without a needle attached. Please dispose of the pen and needle in accordance with local requirements.

How to store the product?

Before use:

- Store the new, unused pen in the refrigerator at 2°C to 8°C (36°F to 46°F)
- If the product is stored outside of refrigeration prior to first use and below temperature of 25°C, it should be used within 30 days.
- Do not freeze the product or use the product if it has been frozen

Pen in use:

- Immediately after dosing and re-attaching the cap to the pen, store the pen in a refrigerator at 2°C to 8°C (36°F to 46°F). Used pens should not be used for dosing after 30 days.
- If the product has been exposed to temperatures above 25°C (77°F), it should not be used.
- Protect the pen from heat and sunlight.
- Keep the pen cap on when your pen is not in use.
- Use a pen for only 30 days.

⚠ **Important Information**

- Always use a new needle for each injection as it will reduce the risk of contamination, infection, leakage, blocked needles & inaccurate dosing. Do not share your pen with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.
- Be careful not to bend or damage the needle.
- Never try to put the inner needle cap back on the needle. You may stick yourself with the needle. Be careful when handling used needles to avoid needle stick injuries.
- If you have dropped your pen against a hard surface or suspect that something is wrong with it, always put on a new disposable needle and check the flow before you inject.
- Do not use the cartridge scale to measure how much Liraglutide to inject – it is not accurate enough.
- Always remove the needle after each injection and store the pen without a needle attached.
- Keep the pen out of reach of others, especially children
- Keep the pen away from dust, dirt and all kinds of liquids. Clean the pen with a cloth moistened with mild detergent. Do not try to wash, soak or lubricate it.

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