SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diavorin 6 mg/ml solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 6 mg of liraglutide produced by chemical synthesis. One pre-filled pen contains 18 mg liraglutide in 3 ml.

Liraglutide, is a human glucagon-like peptide-1 (GLP-1) analogue.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless or almost colourless, isotonic solution; pH=8.15.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diavorin is indicated for the treatment of adults, adolescents and children aged 10 years and above with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology

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.

When Diavorin is added to a sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see section 4.4). Combination therapy with sulfonylurea is only valid for adult patients.

Self-monitoring of blood glucose is not needed in order to adjust the dose of Diavorin . Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Diavorin therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended.

Special populations

Elderly patients (>65 years old)

No dose adjustment is required based on age (see section 5.2).

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 Diavorin is therefore not recommended for use in these patients (see sections 5.1 and 5.2).

Hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Diavorin is not recommended for use in patients with severe hepatic impairment (see section 5.2).

Paediatric population

No dose adjustment is required for adolescents and children aged 10 years and above. No data are available for children below 10 years of age (see sections 5.1 and 5.2).

Method of administration

Diavorin must not be administered intravenously or intramuscularly.
Diavorin 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 Diavorin 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 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).

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 (see sections 4.8 and 5.1).

Thyroid disease

Thyroid adverse events, such as goitre, have been reported in clinical trials and in particular in patients with pre-existing thyroid disease. Liraglutide should therefore be used with caution in these 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 take precautions to avoid fluid depletion.

Excipients

Diavorin contains less than 1 mmol sodium (23 mg) per dose, therefore the medicinal product is essentially ‘sodium-free’.

This medicine contains 42 mg propylene glycol in each 3 ml pre-filled multidose pen which

is equivalent to 14 mg/ml.
If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol.

4.5 Interaction with other medicinal products and other forms of interaction

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 recommended.

Paracetamol

Liraglutide did not change the overall exposure of paracetamol following a single dose of 1000 mg. Paracetamol Cmax was decreased by 31% and median tmax was delayed up to 15 min. No dose adjustment for concomitant use of paracetamol is required.

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 h to 3 h with liraglutide.

Griseofulvin

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%; Cmax decreased by 31%. Digoxin median tmax was delayed from 1 h to 1.5 h. No adjustment of digoxin dose is required based on these results.

Lisinopril

A single dose administration of lisinopril 20 mg with liraglutide resulted in a reduction of lisinopril AUC by 15%; Cmax 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.

Oral contraceptives

Liraglutide lowered ethinyloestradiol and levonorgestrel Cmax by 12 and 13%, respectively, following administration of a single dose of an oral contraceptive product. Tmax was delayed by 1.5 h with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure of either ethinyloestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide.

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.

Paediatric Population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of liraglutide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Liraglutide should not be used during pregnancy, and the use of insulin is recommended instead. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Diavorin should be discontinued.

Breast-feeding

It is not known whether liraglutide is excreted in human milk. Animal studies have shown that the transfer of liraglutide and metabolites of close structural relationship into milk is low. Non-clinical studies have shown a treatment-related reduction of neonatal growth in suckling rat pups (see section 5.3). Because of lack of experience, Diavorin should not be used during breast-feeding.

Fertility

Apart from a slight decrease in the number of live implants, animal studies did not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Diavorin has no or negligible influence on the ability to drive and use machines.

Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Diavorin is used in combination with a sulfonylurea or insulin.

4.8 Undesirable effects

Summary of the safety profile

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

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 more frequently. These reactions usually diminish within a few days or weeks on continued treatment. Headache and 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.

Tabulated list of adverse reactions

Table 1 lists adverse reactions reported in long-term phase 3a controlled trials, the LEADER trial (a long-term cardiovascular outcome trial) and spontaneous (post-marketing) reports. Frequencies for all events have been calculated based on their

incidence in phase 3a clinical trials.
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 1 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	Dysgeusia		
Cardiac disorders		Increased heart rate			
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Dyspepsia Abdominal pain upper Constipation Gastritis Flatulence Abdominal distension Gastroesophageal reflux disease	Delayed gastric emptying	Intestinal obstruction	Pancreatitis (including necrotising pancreatitis)

		Abdominal discomfort Toothache			
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*			

* From controlled phase 3b and 4 clinical trials only where they were measured.

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 episodes 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 antidiabetics other than sulfonylureas. The risk of hypoglycaemia is low with combined use of basal insulin and liraglutide (1.0 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 rate ratio 0.69 [0.51 to 0.93]) (see section 5.1). For patients treated with premix insulin at baseline and at least for the following 26 weeks, the rate of severe hypoglycaemia for both liraglutide and placebo was 2.2 events per 100 patient years.

Gastrointestinal adverse reactions

When combining liraglutide with metformin, 20.7% 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, 9.1% 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 continued therapy, 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 3a clinical trials with liraglutide. In the LEADER trial, the frequency of cholelithiasis and cholecystitis was 1.5% and 1.1% for liraglutide and 1.1% and 0.7% for placebo, respectively (see section 5.1).

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 (26 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 Diavorin in long- term (26 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 Diavorin. 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 5.1).

Allergic reactions

Allergic reactions including urticaria, rash and pruritus have been reported from marketed use of Diavorin.
Few cases of anaphylactic reactions with additional symptoms such as hypotension, palpitations, dyspnoea and oedema have been reported with marketed use of Diavorin. Few cases (0.05%) of angioedema have been reported during all long-term clinical trials with Diavorin.

4.9 Overdose

From clinical trials and marketed use, overdoses have been reported of up to 40 times (72 mg) the recommended maintenance dose. Events reported included severe nausea, vomiting, diarrhoea and severe hypoglycaemia.

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. The patient should be observed for clinical signs of dehydration and blood glucose should be monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, glucagon-like peptide-1 (GLP-1) analogues. ATC code: A10BJ02

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 from the

pancreatic beta cells. Unlike native GLP-1, liraglutide has a pharmacokinetic and pharmacodynamic profile in humans suitable for once daily administration. Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption; binding to albumin; and higher enzymatic stability towards the dipeptidyl peptidase -4 (DPP-4) and neutral endopeptidase (NEP) enzymes, 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. Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucose-dependent manner. 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 minor delay in gastric emptying. Liraglutide reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake, GLP-1 is a physiological regulator of appetite and food intake, but the exact mechanism of action is not entirely clear.

In animal studies, peripheral administration of liraglutide led to uptake in specific brain regions involved in regulation of appetite, where liraglutide via specific activation of the GLP-1 receptor (GLP-1R) increased key satiety and decreased key hunger signals, thereby leading to lower body weight.

GLP-1 receptors are also expressed in specific locations in the heart, vasculature, immune system, and kidneys. In mouse models of atherosclerosis, liraglutide prevented aortic plaque progression and reduced inflammation in the plaque. In addition, liraglutide had a beneficial effect on plasma lipids.
Liraglutide did not reduce the plaque size of already established plaques.

Pharmacodynamic effects
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

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 3a adult trials were conducted to evaluate the effects of liraglutide on glycaemic control (Table 2). Treatment with liraglutide produced clinically and statistically significant improvements in glycosylated haemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose and postprandial glucose compared with placebo.

These trials included 3,978 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 (66 treated with liraglutide) were ≥75 years of age.

Additional trials were conducted with liraglutide that included 1,901 patients in four unblinded, randomised, controlled clinical trials (including 464, 658, 323 and 177 patients per 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 HbA_{1c} compared with glimepiride 8 mg (-0.84% for 1.2 mg, -1.14% for 1.8 mg vs -0.51% for comparator) in patients previously treated with either diet and exercise or OAD monotherapy at no more than half-maximal dose (Table 2).

Combination with oral antidiabetics

Liraglutide in combination therapy, for 26 weeks, with metformin, glimepiride or metformin and rosiglitazone or SGLT2i ± metformin resulted in statistically significant and sustained reductions in HbA_{1c} compared with patients receiving placebo (Table 2).

Table 2 Liraglutide clinical phase 3 trials in monotherapy (52 weeks) and in combination with oral antidiabetics (26 weeks)

	N	Mean baseline HbA_{1c} (%)	Mean HbA_{1c} change from baseline (%)	Patients (%) achieving HbA_{1c}<7%	Mean baseline weight (kg)	Mean weight change from baseline (kg)
Monotherapy						
Liraglutide 1.2 mg	251	8.18	-0.84*	42.8[1], 58.3[3]	92.1	-2.05**
Liraglutide 1.8 mg	246	8.19	-1.14**	50.9[1], 62.0[3]	92.6	-2.45**
Glimepiride 8 mg/day	248	8.23	-0.51	27.8[1], 30.8[3]	93.3	1.12
Add-on to metformin (2,000 mg/day)						
Liraglutide 1.2 mg	240	8.3	-0.97†	35.3[1], 52.8[2]	88.5	-2.58**
Liraglutide 1.8 mg	242	8.4	-1.00†	42.4[1], 66.3[2]	88.0	-2.79**
Placebo	121	8.4	0.09	10.8[1], 22.5[2]	91.0	-1.51
Glimepiride 4 mg/day	242	8.4	-0.98	36.3[1], 56.0[2]	89.0	0.95
Add-on to glimepiride (4 mg/day)						
Liraglutide 1.2 mg	228	8.5	-1.08**	34.5[1], 57.4[2]	80.0	0.32**
Liraglutide 1.8 mg	234	8.5	-1.13**	41.6[1], 55.9[2]	83.0	-0.23**
Placebo	114	8.4	0.23	7.5[1], 11.8[2]	81.9	-0.10
Rosiglitazone 4 mg/day	231	8.4	-0.44	21.9[1], 36.1[2]	80.6	2.11
Add-on to metformin (2,000 mg/day) + rosiglitazone (4 mg twice daily)						
Liraglutide 1.2 mg	177	8.48	-1.48	57.5[1]	95.3	-1.02
Liraglutide 1.8 mg	178	8.56	-1.48	53.7[1]	94.9	-2.02
Placebo	175	8.42	-0.54	28.1[1]	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[1]	85.8	-1.81**
Placebo	114	8.3	-0.24	15.3[1]	85.4	-0.42
Insulin glargine[4]	232	8.1	-1.09	45.8[1]	85.2	1.62
Add-on to SGLT2i[5] ± metformin (≥1500 mg/day)						
Liraglutide 1.8 mg	203	8.00	-1.02***	54.8***	91.0	-2.92
Placebo	100	7.96	-0.28	13.9	91.4	-2.06

*Superiority ($p<0.01$) vs active comparator; **Superiority ($p<0.0001$) vs active comparator; ***Superiority ($p<0.001$) vs active comparator, †Non-inferiority ($p<0.0001$) vs active comparator

[1]all patients; [2]previous OAD monotherapy; [3]previous diet treated patients

[5]Liraglutide add-on to SGLT2i was investigated at all approved doses of SGLT2i

[4]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 FPG	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[a]
≥6.7 mmol/l (≥120 mg/dl)	2 IU

[a] According to the individualised recommendation by the investigator at the previous visit, for example

depending on 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 degludec in combination with metformin achieved a target HbA_{1c} <7% and the remaining patients continued in a 26-week open label trial and were randomised to add liraglutide or a single dose of insulin aspart (with the largest meal). In the insulin degludec + liraglutide arm, the insulin dose was reduced by 20% in order to minimize the risk of hypoglycaemia. Addition of liraglutide resulted in a statistically significantly greater reduction of HbA_{1c} (-0.73% for liraglutide vs -0.40% for comparator) and body weight (-3.03 vs 0.72 kg). The rate of hypoglycaemic episodes (per patient year of exposure) was statistically significantly lower when adding liraglutide compared to adding a single dose of insulin aspart (1.0 vs 8.15; ratio: 0.13; 95% CI: 0.08 to 0.21).

In a 52-week clinical trial, the addition of insulin detemir to liraglutide 1.8 mg and metformin in patients not achieving glycaemic targets on liraglutide and metformin alone resulted in a HbA_{1c} decrease from baseline of 0.54%, 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 (0.23 versus 0.03 events per patient years).

In the LEADER trial, (see subsection Cardiovascular evaluation), 873 patients were on premix insulin (with or without OAD(s)) at baseline and at least for the following 26 weeks. The mean HbA_{1c} at baseline was 8.7% for liraglutide and placebo. At week 26, the estimated mean change in HbA_{1c}
was -1.4% and -0.5% for liraglutide and placebo, respectively, with an estimated treatment difference of -0.9 $[-1.00; -0.70]_{95\% \text{ CI}}$. 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 treatment in reducing HbA_{1c} after 26 weeks (-1.05% vs -0.38%). Significantly more patients achieved HbA_{1c} below 7% with liraglutide compared with placebo (52.8% vs 19.5%). 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 HbA_{1c}

Liraglutide alone resulted in a statistically significant greater proportion of patients achieving HbA_{1c}
≤6.5% at 52 weeks compared with patients receiving glimepiride (37.6% for 1.8 mg and 28.0% for 1.2 mg vs 16.2% for comparator).

Liraglutide in combination with metformin, glimepiride, metformin and rosiglitazone or SGLT2i ± metformin resulted in a statistically significant greater proportion of patients achieving an HbA_{1c}
≤6.5% at 26 weeks compared with patients receiving these agents 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 13–43.5 mg/dl (0.72–2.42 mmol/l). This reduction was observed within the first two 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 after 52 weeks treatment with liraglutide was demonstrated in a subset of patients with type 2 diabetes (n=29).

- Body weight

Treatment with liraglutide in combination with metformin, metformin and glimepiride, metformin and rosiglitazone or SGLT2i with or without metformin was associated with a sustained weight reduction in the range from 0.86 kg to 2.62 kg compared with placebo.

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

- Cardiovascular evaluation

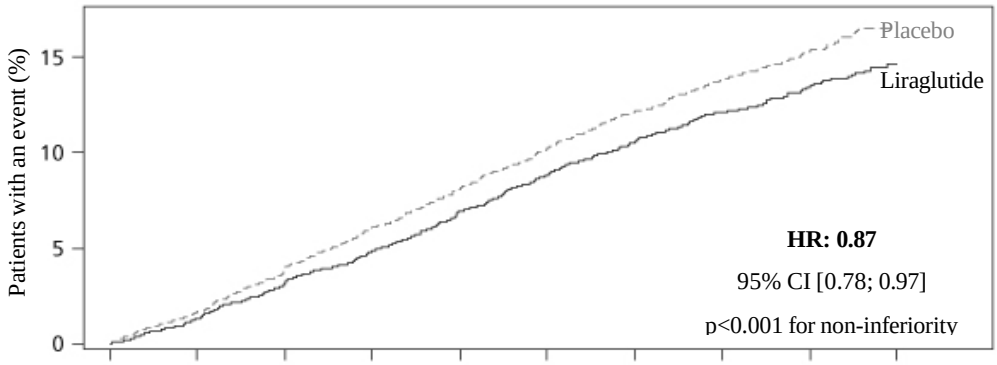
Post-hoc analysis of serious major adverse cardiovascular events (cardiovascular death, myocardial infarction, stroke) from all intermediate and long-term phase 2 and 3 trials (ranging from 26 and up to 100 weeks duration) including 5,607 patients (3,651 exposed to liraglutide), showed no increase in cardiovascular risk (incidence ratio of 0.75 (95% CI 0.35; 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 HbA_{1c} and cardiovascular (CV) risk factors. Primary outcome or vital status at end of trial was available for 99.7% and 99.6% of participants randomised to liraglutide and placebo, respectively. The duration of observation was a minimum of 3.5 years and up to a maximum of 5 years. The study population included patients ≥65 years (n=4,329) and ≥75 years (n=836) and patients with mild (n=3,907), moderate (n=1,934) or severe (n=224) renal impairment. The mean age was 64 years and the mean BMI was 32.5 kg/m². The mean duration of diabetes was 12.8 years.

The primary endpoint was the time from randomisation to first occurrence of any major adverse cardiovascular events (MACE): CV death, non-fatal myocardial infarction or non-fatal stroke. Liraglutide was superior in preventing MACE vs placebo (Figure 1). The estimated hazard ratio was consistently below 1 for all 3 MACE components.

Liraglutide also significantly reduced the risk of expanded MACE (primary MACE, unstable angina pectoris leading to hospitalisation, coronary revascularisation, or hospitalisation due to heart failure) and other secondary endpoints (Figure 2).

Figure 1: Kaplan Meier plot of time to first MACE – FAS population

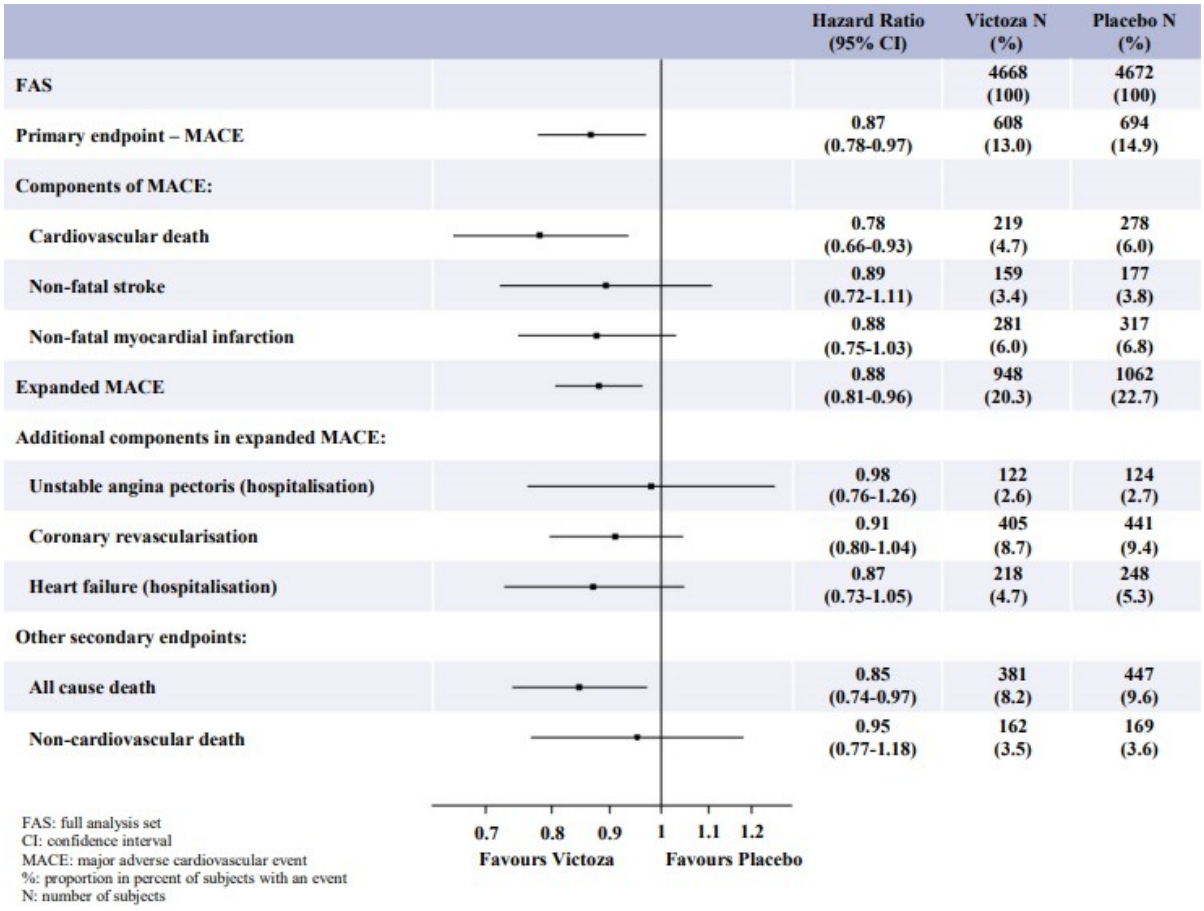


Patients at risk

Placebo	4672	4587	4473	4352	4237	4123	4010	3914	1543	407
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424

FAS: full analysis set.

Figure 2: Forest plot of analyses of individual cardiovascular event types – FAS population



A significant and sustained reduction in HbA_{1c} from baseline to month 36 was observed with liraglutide vs placebo, in addition to standard of care (-1.16% vs -0.77%; estimated treatment difference [ETD] -0.40% [-0.45; -0.34]). The need for treatment intensification with insulin was reduced by 48% with liraglutide vs placebo in insulin-naive patients at baseline (HR 0.52 [0.48; 0.57]).

- Blood pressure and heart rate

Over the duration of the phase 3a trials, liraglutide decreased the systolic blood pressure on average of 2.3 to 6.7 mmHg from baseline and compared to active comparator the decrease was 1.9 to 4.5 mmHg. A mean increase in heart rate from baseline of 2 to 3 beats per minute has been observed with liraglutide in long-term clinical trials including LEADER. In the LEADER trial, no long-term clinical impact of increased heart rate on the risk of cardiovascular events was observed.

- Microvascular evaluation

In the LEADER trial, microvascular events comprised nephropathy and retinopathy outcomes. The analysis of time to first microvascular event for liraglutide vs placebo had a HR of 0.84 [0.73, 0.97]. The HR for liraglutide vs placebo was 0.78 [0.67, 0.92] for time to first nephropathy event and 1.15 [0.87, 1.52] for time to first retinopathy event.

- Immunogenicity

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, 8.6% of patients developed antibodies. Antibody formation has not been associated with reduced efficacy of liraglutide.

Paediatric population

In a double-blind study comparing the efficacy and safety of liraglutide 1.8 mg versus placebo as add-on to metformin ± insulin in adolescents and children aged 10 years and above with type 2 diabetes, liraglutide was superior to placebo treatment in reducing HbA_{1c} after 26 weeks (-1.06, [-1.65, 0.46]). The treatment difference in HbA_{1c} was 1.3% after additional 26 weeks of open label extension, confirming the sustained glycaemic control with liraglutide injection.

The efficacy and safety profile of liraglutide was comparable to that observed in the adult population treated with liraglutide. Based on adequate glycaemic control or tolerability, 30% of trial subjects remained on a dose of 0.6 mg, 17% escalated to a dose of 1.2 mg and 53% escalated to a dose of 1.8 mg.

5.2 Pharmacokinetic properties

Absorption

The absorption of liraglutide following subcutaneous administration is slow, reaching maximum concentration 8–12 hours post dosing. Estimated maximum liraglutide concentration was 9.4 nmol/l (mean body weight approximately 73 kg) for a subcutaneous single dose of liraglutide 0.6 mg. At

1.8 mg liraglutide, the average steady state concentration of liraglutide ($AUC_{\tau}/24$) reached approximately 34 nmol/l (mean body weight approximately 76 kg). The exposure of liraglutide decreases with increasing body weight. Liraglutide exposure increased proportionally with dose. The intra-subject coefficient of variation for liraglutide AUC was 11% following single dose administration.

Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution

The apparent volume of distribution after subcutaneous administration is 11–17 l. The mean volume of distribution after intravenous administration of liraglutide is 0.07 l/kg. Liraglutide is extensively bound to plasma proteins (>98%).

Biotransformation

During 24 hours following administration of a single radiolabelled [^{3}H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected (≤9% and ≤5% of total plasma radioactivity exposure). Liraglutide is metabolised in a similar manner to large proteins without a specific organ having been identified as major route of elimination.

Elimination

Following a [^{3}H]-liraglutide dose, intact liraglutide was not detected in urine or faeces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or faeces (6% and 5%, respectively). The urine and faeces radioactivity was mainly excreted during the first 6– 8 days, and corresponded to three minor metabolites, respectively.

The mean clearance following subcutaneous administration of a single dose liraglutide is approximately 1.2 l/h with an elimination half-life of approximately 13 hours.

Special populations

Elderly patients

Age had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results from a pharmacokinetic study in healthy subjects and population pharmacokinetic data analysis of patients (18 to 80 years).

Gender

Gender had no clinically meaningful effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic data analysis of male and female patients and a pharmacokinetic study in healthy subjects.

Ethnic origin

Ethnic origin had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic analysis which included patients of White, Black, Asian and Hispanic groups.

Obesity

Population pharmacokinetic analysis suggests that body mass index (BMI) has no significant effect on the pharmacokinetics of liraglutide.

Hepatic impairment

The pharmacokinetics of liraglutide was evaluated in patients with varying degree of hepatic impairment in a single-dose trial. Liraglutide exposure was decreased by 13-23% in patients with mild to moderate hepatic impairment compared to healthy subjects.

Exposure was significantly lower (44%) in patients with severe hepatic impairment (Child Pugh score >9).

Renal impairment

Liraglutide exposure was reduced in patients with renal impairment compared to individuals with normal renal function. Liraglutide exposure was lowered by 33%, 14%, 27% and 26% in patients with mild (creatinine clearance, CrCl 50–80 ml/min), moderate (CrCl 30–50 ml/min), and severe (CrCl

<30 ml/min) renal impairment and in end-stage renal disease requiring dialysis, respectively.

Similarly, in a 26-week clinical trial, patients with type 2 diabetes and moderate renal impairment (CrCL 30–59 ml/min, see section 5.1) had 26% lower liraglutide exposure when compared with a separate trial including patients with type 2 diabetes with normal renal function or mild renal impairment.

Paediatric population

Pharmacokinetic properties were assessed in clinical studies in the paediatric population with type 2 diabetes aged 10 years and above. The liraglutide exposure in adolescents and children was comparable to that observed in the adult population.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity.

Non-lethal thyroid C-cell tumours were seen in 2-year carcinogenicity studies in rats and mice. In rats, a no observed adverse effect level (NOAEL) was not observed. These tumours were not seen in monkeys treated for 20 months. These findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot be completely excluded. No other treatment-related tumours have been found.

Animal studies did not indicate direct harmful effects with respect to fertility but slightly increased early embryonic deaths at the highest dose. Dosing with liraglutide during mid-gestation caused a reduction in maternal weight and foetal growth with equivocal effects on ribs in rats and skeletal variation in the rabbit. Neonatal growth was reduced in rats while exposed to liraglutide, and persisted in the post-weaning period in the high dose group. It is unknown whether the reduced pup growth is caused by reduced pup milk intake due to a direct GLP-1 effect or reduced maternal milk production due to decreased caloric intake.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate

Propylene glycol

Phenol

Water for injections

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

24 months.

After first use: 1 month.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C). Do not freeze.

Store away from the freezer compartment.

After first use: Store below 30°C or store in a refrigerator (2°C–8°C). Do not freeze.

Keep the cap on the pen in order to protect from light.

6.5 Nature and contents of container

Cartridge (type 1 glass) with a plunger (bromobutyl) with round shaped aluminium lined seal contained in a pre-filled multidose 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 sizes of 1, 2, 3, 5 or 10 pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Diavorin should not be used if it does not appear clear and colourless or almost colourless. Diavorin should not be used if it has been frozen.

Diavorin can be administered with needles up to a length of 8 mm and as thin as 32G. The pen is designed to be used with BD Ultra-Fine™ disposable needles or NovoFine® disposable 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.

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

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24/04/2025