Liraglutide lowers body weight in humans mainly through loss of fat mass with relative reductions in visceral fat being greater than for subcutaneous fat loss. Liraglutide regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and prospective food consumption, thereby leading to reduced food intake. Liraglutide does not increase energy expenditure compared to placebo.

Liraglutide stimulates insulin secretion and lowers glucagon secretion in a glucose-dependent manner which results in a lowering of fasting and post-prandial glucose. The glucose-lowering effect is more pronounced in patients with prediabetes and diabetes compared to patients with normoglycaemia. Clinical trials suggest that liraglutide improves and sustains beta-cell function, according to HOMA-B and the proinsulin-to-insulin ratio.

Clinical efficacy and safety

The efficacy and safety of liraglutide for weight management in conjunction with reduced calorie intake and increased physical activity were studied in four phase 3 randomised, double-blind, placebo-controlled trials which included a total of 5,358 adult patients.

- **Trial 1 (SCALE Obesity & Pre-Diabetes - 1839):** A total of 3,731 patients with obesity (BMI ≥30 kg/m²) or with overweight (BMI ≥27 kg/m²) with dyslipidaemia and/or hypertension were stratified according to prediabetes status at screening and BMI at baseline (≥30 kg/m² or <30 kg/m²). All 3,731 patients were randomised to 56 weeks of treatment and the 2,254 patients with prediabetes at screening were randomised to 160 weeks of treatment. Both treatment periods were followed by a 12-week off drug/placebo observational follow-up period. Lifestyle intervention in the form of an energy-restricted diet and exercise counselling was background therapy for all patients.
  The 56-week part of trial 1 assessed body weight loss in all the 3,731 randomised patients (2,590 completers).
  The 160-week part of trial 1 assessed time to onset of type 2 diabetes in the 2,254 randomised patients with prediabetes (1,128 completers).
- **Trial 2 (SCALE Diabetes - 1922):** A 56-week trial assessing body weight loss in 846 randomised (628 completers) obese and overweight patients with insufficiently controlled type 2 diabetes mellitus (HbA_{1c} range 7–10%). The background treatment at trial start was either diet and exercise alone, metformin, a sulfonylurea, a glitazone as single agents or any combination hereof.
- **Trial 3 (SCALE Sleep Apnoea - 3970):** A 32-week trial assessing sleep apnoea severity and body weight loss in 359 randomised (276 completers) obese patients with moderate or severe obstructive sleep apnoea.
- **Trial 4 (SCALE Maintenance - 1923):** A 56-week trial assessing body weight maintenance and weight loss in 422 randomised (305 completers) obese and overweight patients with hypertension or dyslipidaemia after a preceding weight loss of ≥5% induced by a low-calorie diet.

Body weight

Superior weight loss was achieved with liraglutide compared to placebo in obese/overweight patients in all groups studied. Across the trial populations, greater proportions of the patients achieved ≥5% and >10% weight loss with liraglutide than with placebo (tables 4–6). In the 160-weeks part of trial 1, the weight loss occurred mainly in the first year and was sustained throughout 160 weeks. In trial 4, more patients maintained the weight loss achieved prior to treatment initiation with liraglutide than with placebo (81.4% and 48.9%, respectively). Specific data on weight loss, responders, time course and cumulative distribution of weight change (%) for trials 1–4 are presented in tables 4–8 and figures 1, 2 and 3.

Weight loss response after 12 weeks with liraglutide (3.0 mg) treatment

Early responders were defined as patients who achieved ≥5% weight loss after 12 weeks on treatment dose of liraglutide (4 weeks of dose escalation and 12 weeks on treatment dose). In the 56-week part of trial 1, 67.5% achieved ≥5% weight loss after 12 weeks. In trial 2, 50.4% achieved ≥5% weight loss after 12 weeks. With continued treatment with liraglutide, 86.2% of these early responders are predicted to achieve a weight loss of ≥5% and 51% are predicted to achieve a weight loss of ≥10% after 1 year of treatment. The predicted mean weight loss in early responders who complete 1 year of treatment is 11.2% of their baseline body weight (9.7% for males and 11.6% for females). For patients who have achieved a weight loss of <5% after 12 weeks on treatment dose of liraglutide, the proportion of patients not reaching a weight loss of ≥10% after 1 year is 93.4%.

Glycaemic control

Treatment with liraglutide significantly improved glycaemic parameters across sub-populations with normoglycaemia, prediabetes and type 2 diabetes mellitus. In the 56-week part of trial 1, fewer patients treated with liraglutide had developed type 2 diabetes mellitus compared to patients treated with placebo (0.2% vs. 1.1%). More patients with prediabetes at baseline had reversed their prediabetes compared to patients treated with placebo (69.2% vs. 32.7%). In the 160-week part of trial 1, the primary efficacy endpoint was the proportion of patients with onset of type 2 diabetes mellitus evaluated as time to onset. At week 160, while on treatment, 3% treated with Saxenda and 11% treated with placebo were diagnosed with type 2 diabetes mellitus. The estimated time to onset of type 2 diabetes mellitus for patients treated with liraglutide 3.0 mg was 2.7 times longer (with a 95% confidence interval of [1.9, 3.9]), and the hazard ratio for risk of developing type 2 diabetes mellitus was 0.2 for liraglutide versus placebo.

Cardiometabolic risk factors

Treatment with liraglutide significantly improved systolic blood pressure and waist circumference compared with placebo (tables 4, 5 and 6).

Apnoea-Hypopnoea Index (AHI)

Treatment with liraglutide significantly reduced the severity of obstructive sleep apnoea as assessed by change from baseline in the AHI compared with placebo (table 7).

Table 4 Trial 1: Changes from baseline in body weight, glycaemia and cardiometabolic parameters at week 56

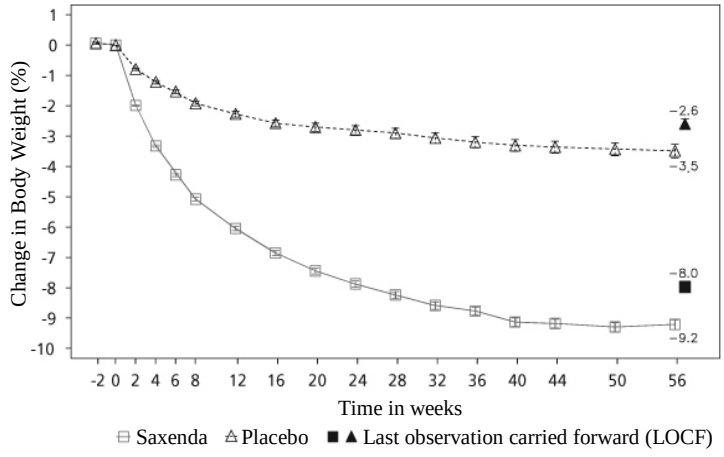
	Saxenda (N=2437)		Placebo (N=1225)		Saxenda vs. placebo
Body weight					
Baseline, kg (SD)	106.3 (21.2)		106.3 (21.7)		-
Mean change at week 56, % (95% CI)	-8.0		-2.6		-5.4** (-5.8; -5.0)
Mean change at week 56, kg (95% CI)	-8.4		-2.8		-5.6** (-6.0; -5.1)
Proportion of patients losing ≥5% body weight at week 56, % (95% CI)	63.5		26.6		4.8** (4.1; 5.6)
Proportion of patients losing >10% body weight at week 56, % (95% CI)	32.8		10.1		4.3** (3.5; 5.3)
Glycaemia and cardiometabolic factors	Baseline	Change	Baseline	Change	
HbA_{1c}, %	5.6	-0.3	5.6	-0.1	-0.23** (-0.25; -0.21)
FPG, mmol/L	5.3	-0.4	5.3	-0.01	-0.38** (-0.42; -0.35)
Systolic blood pressure, mmHg	123.0	-4.3	123.3	-1.5	-2.8** (-3.6; -2.1)
Diastolic blood pressure, mmHg	78.7	-2.7	78.9	-1.8	-0.9* (-1.4; -0.4)
Waist circumference, cm	115.0	-8.2	114.5	-4.0	-4.2** (-4.7; -3.7)

Full Analysis Set. For body weight, HbA_{1c}, FPG, blood pressure and waist circumference, baseline values are means, changes from baseline at week 56 are estimated means (least-squares) and treatment contrasts at week 56 are estimated treatment differences. For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. Missing post-baseline values were imputed using the last observation carried forward.
* p<0.05. ** p<0.0001. CI=confidence interval. FPG=fasting plasma glucose. SD=standard deviation.

Table 5 Trial 1: Changes from baseline in body weight, glycaemia and cardiometabolic parameters at week 160

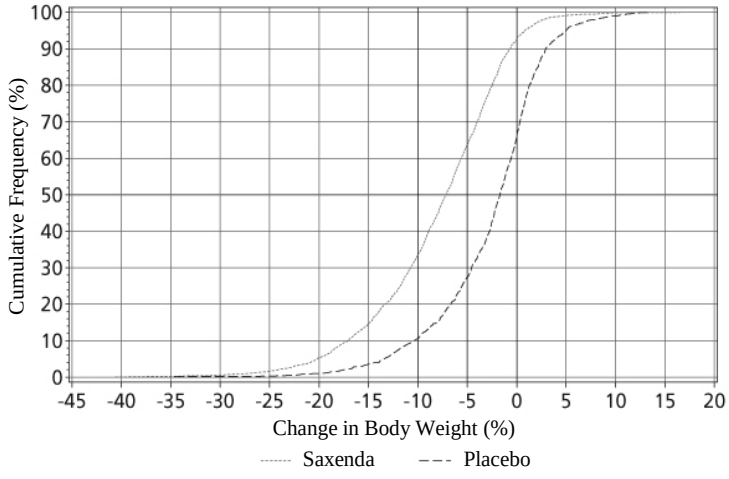
	Saxenda (N=1472)		Placebo (N=738)		Saxenda vs. placebo
Body weight					
Baseline, kg (SD)	107.6 (21.6)		108.0 (21.8)		
Mean change at week 160, % (95% CI)	-6.2		-1.8		-4.3** (-4.9; -3.7)
Mean change at week 160, kg (95% CI)	-6.5		-2.0		-4.6** (-5.3; -3.9)
Proportion of patients losing ≥5% body weight at week 160, % (95% CI)	49.6		23.4		3.2** (2.6; 3.9)
Proportion of patients losing >10% body weight at week 160, % (95% CI)	24.4		9.5		3.1** (2.3; 4.1)
Glycaemia and cardiometabolic factors	Baseline	Change	Baseline	Change	
HbA_{1c}, %	5.8	-0.4	5.7	-0.1	-0.21** (-0.24; -0.18)
FPG, mmol/L	5.5	-0.4	5.5	0.04	-0.4** (-0.5; -0.4)
Systolic blood pressure, mmHg	124.8	-3.2	125.0	-0.4	-2.8** (-3.8; -1.8)
Diastolic blood pressure, mmHg	79.4	-2.4	79.8	-1.7	-0.6 (-1.3; 0.1)
Waist circumference, cm	116.6	-6.9	116.7	-3.4	-3.5** (-4.2; -2.8)

Full Analysis Set. For body weight, HbA_{1c}, FPG, blood pressure and waist circumference, baseline values are means, changes from baseline at week 160 are estimated means (least-squares) and treatment contrasts at week 160 are estimated treatment differences. For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. Missing post-baseline values were imputed using the last observation carried forward.
** p<0.0001. CI=confidence interval. FPG=fasting plasma glucose. SD=standard deviation.



Observed values for patients completing each scheduled visit

Figure 1 Change from baseline in body weight (%) by time in trial 1 (0–56 weeks)



Last observation carried forward.

Figure 2 Cumulative distribution of weight change (%) after 56 weeks of treatment in trial 1

Table 6 Trial 2: Changes from baseline in body weight, glycaemia and cardiometabolic parameters at week 56

	Saxenda (N=412)		**Placebo (N=211)**		**Saxenda vs. placebo**
Body weight					
Baseline, kg (SD)	105.6 (21.9)		106.7 (21.2)		-
Mean change at week 56, % (95% CI)	-5.9		-2.0		-4.0** (-4.8; -3.1)
Mean change at week 56, kg (95% CI)	-6.2		-2.2		-4.1** (-5.0; -3.1)
Proportion of patients losing ≥5% body weight at week 56, % (95% CI)	49.8		13.5		6.4** (4.1; 10.0)
Proportion of patients losing >10% body weight at week 56, % (95% CI)	22.9		4.2		6.8** (3.4; 13.8)
Glycaemia and cardiometabolic factors	Baseline	Change	Baseline	Change	
HbA_{1c}, %	7.9	-1.3	7.9	-0.4	-0.9** (-1.1; -0.8)
FPG, mmol/L	8.8	-1.9	8.6	-0.1	-1.8** (-2.1; -1.4)
Systolic blood pressure, mmHg	128.9	-3.0	129.2	-0.4	-2.6* (-4.6; -0.6)
Diastolic blood pressure, mmHg	79.0	-1.0	79.3	-0.6	-0.4 (-1.7; 1.0)
Waist circumference, cm	118.1	-6.0	117.3	-2.8	-3.2** (-4.2; -2.2)

Full Analysis Set. For body weight, HbA_{1c}, FPG, blood pressure and waist circumference, baseline values are means, changes from baseline at week 56 are estimated means (least-squares) and treatment contrasts at week 56 are estimated treatment differences. For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. Missing post-baseline values were imputed using the last observation carried forward.
* p<0.05. ** p<0.0001. CI=confidence interval. FPG=fasting plasma glucose. SD=standard deviation.

Table 7 Trial 3: Changes from baseline in body weight and Apnoea-Hypopnoea Index at week 32

	Saxenda (N=180)		**Placebo (N=179)**		**Saxenda vs. placebo**
Body weight					
Baseline, kg (SD)	116.5 (23.0)		118.7 (25.4)		-
Mean change at week 32, % (95% CI)	-5.7		-1.6		-4.2** (-5.2; -3.1)
Mean change at week 32, kg (95% CI)	-6.8		-1.8		-4.9** (-6.2; -3.7)
Proportion of patients losing ≥5% body weight at week 32, % (95% CI)	46.4		18.1		3.9** (2.4; 6.4)
Proportion of patients losing >10% body weight at week 32 % (95% CI)	22.4		1.5		19.0** (5.7; 63.1)
	Baseline	Change	Baseline	Change	
Apnoea-Hypopnoea Index, events/hour	49.0	-12.2	49.3	-6.1	-6.1* (-11.0; -1.2)

Full Analysis Set. Baseline values are means, changes from baseline at week 32 are estimated means (least-squares) and treatment contrasts at week 32 are estimated treatment differences (95% CI). For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. Missing post-baseline values were imputed using the last observation carried forward. * p<0.05. ** p<0.0001. CI=confidence interval. SD=standard deviation.

Table 8 Trial 4: Changes from baseline in body weight at week 56

	Saxenda (N=207)	**Placebo (N=206)**	**Saxenda vs. placebo**
Baseline, kg (SD)	100.7 (20.8)	98.9 (21.2)	-
Mean change at week 56, % (95% CI)	-6.3	-0.2	-6.1** (-7.5; -4.6)
Mean change at week 56, kg (95% CI)	-6.0	-0.2	-5.9** (-7.3; -4.4)
Proportion of patients losing ≥5% body weight at week 56, % (95% CI)	50.7	21.3	3.8** (2.4; 6.0)
Proportion of patients losing >10% body weight at week 56, % (95% CI)	27.4	6.8	5.1** (2.7; 9.7)

Full Analysis Set. Baseline values are means, changes from baseline at week 56 are estimated means (least-squares) and treatment contrasts at week 56 are estimated treatment differences. For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. Missing post-baseline values were imputed using the last observation carried forward. ** p<0.0001. CI=confidence interval. SD=standard deviation.

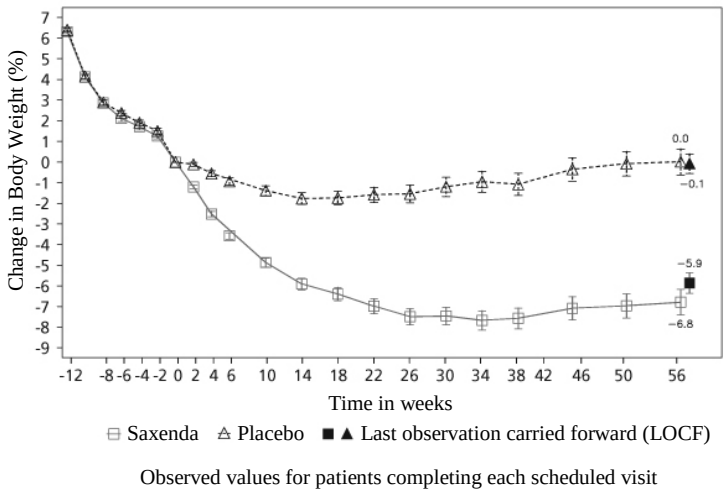


Figure 3 Change from randomisation (week 0) in body weight (%) by time in trial 4

Before week 0 patients were only treated with low-calorie diet and exercise. At week 0 patients were randomised to receive either Saxenda or placebo.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-liraglutide antibodies following treatment with liraglutide. In clinical trials, 2.5% of patients treated with liraglutide developed anti-liraglutide antibodies. Antibody formation has not been associated with reduced efficacy of liraglutide.

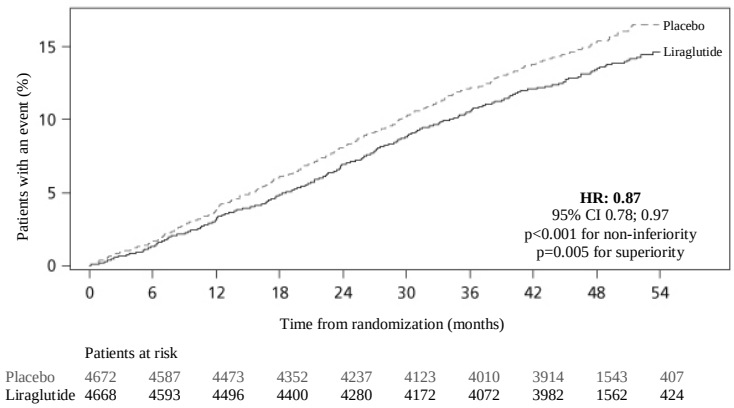
Cardiovascular evaluation

Major adverse cardiovascular events (MACE) were adjudicated by an external independent group of experts and defined as non-fatal myocardial infarction, non-fatal stroke and cardiovascular death. In all the long-term clinical trials with Saxenda, there were 6 MACE for patients treated with liraglutide and 10 MACE for placebo-treated patients. The hazard ratio and 95% CI is 0.33 [0.12; 0.90] for liraglutide versus placebo. A mean increase in heart rate from baseline of 2.5 beats per minute (ranging across trials from 1.6 to 3.6 beats per minute) has been observed with liraglutide in clinical phase 3 trials. The heart rate peaked after approximately 6 weeks. The long-term clinical impact of this mean increase in heart rate has not been established. The change in heart rate was reversible upon discontinuation of liraglutide (see section 4.4).

The Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcomes Results (LEADER) trial included 9,340 patients with insufficiently controlled type 2 diabetes. The vast majority of these had established cardiovascular disease. Patients were randomly allocated to either liraglutide on a daily dose of up to 1.8 mg (4,668) or placebo (4,672), both on a background of standard of care.

The duration of exposure was between 3.5 and 5 years. The mean age was 64 years and the mean BMI was 32.5 kg/m². Mean baseline HbA_{1c} was 8.7 and had improved after 3 years by 1.2 % in patients assigned to liraglutide and by 0.8 % in patients assigned to placebo. The primary endpoint was the time from randomisation to first occurrence of any major adverse cardiovascular events (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

Liraglutide significantly reduced the rate of major adverse cardiovascular events (primary endpoint events, MACE) vs. placebo (3.41 vs. 3.90 per 100 patient years of observation in the liraglutide and placebo groups, respectively) with a risk reduction of 13%, HR 0.87, [0.78, 0.97] [95% CI]) (p=0.005) (see figure 4).



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 4 Kaplan Meier plot of time to first MACE – FAS population

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Saxenda in one or more subsets of the paediatric population in the treatment of obesity and in the treatment of Prader-Willi Syndrome (see section 4.2 for information on paediatric use).

In a double-blind trial comparing the efficacy and safety of Saxenda versus placebo on weight loss in adolescent patients aged 12 years and above with obesity, Saxenda was superior to placebo in weight reduction (evaluated as BMI Standard Deviation Score) after 56 weeks of treatment (table 9).
A greater proportion of the patients achieved ≥5% and ≥10% reductions in BMI with liraglutide than with placebo, as well as greater reductions in mean BMI and body weight (table 9). After 26 weeks of off-trial product follow-up period, weight regain was observed with liraglutide vs placebo (table 9).

Table 9 Trial 4180: Changes from baseline in body weight and BMI at week 56 and change in BMI SDS from week 56 to week 82

	Saxenda (N=125)	**Placebo (N=126)**	**Saxenda vs. placebo**
BMI SDS			
Baseline, BMI SDS (SD)	3.14 (0.65)	3.20 (0.77)	
Mean change at week 56 (95% CI)	-0.23	-0.00	-0.22* (-0.37; -0.08)
Week 56, BMI SDS (SD)	2.88 (0.94)	3.14 (0.98)	
Mean change from week 56 to week 82, BMI SDS (95% CI)	0.22	0.07	0.15** (0.07; 0.23)
Body weight			
Baseline, kg (SD)	99.3 (19.7)	102.2 (21.6)	-
Mean change at week 56, % (95% CI)	-2.65	2.37	-5.01** (-7.63; -2.39)
Mean change at week 56, kg (95% CI)	-2.26	2.25	-4.50** (-7.17; -1.84)
BMI			
Baseline, kg/m^2 (SD)	35.3 (5.1)	35.8 (5.7)	-
Mean change at week 56, kg/m^2 (95% CI)	-1.39	0.19	-1.58** (-2.47; -0.69)
Proportion of patients with ≥5% reduction in baseline BMI at week 56, % (95% CI)	43.25	18.73	3.31** (1.78; 6.16)

Proportion of patients with ≥10% reduction in baseline BMI at week 56, % (95% CI)	26.08	8.11	4.00** (1.81; 8.83)

Full Analysis Set. For BMI SDS, body weight and BMI, baseline values are means, changes from baseline at week 56 are estimated means (least-squares) and treatment contrasts at week 56 are estimated treatment differences. For BMI SDS, value at week 56 are means, changes from week 56 to week 82 are estimated means (least-squares) and treatment contrasts at week 82 are estimated treatment differences. For the proportions of patients losing ≥5%/≥10% baseline BMI, estimated odds ratios are presented. Missing observations were imputed from the placebo arm based on a jump to reference multiple (x100) imputation approach.
*p<0.01, **p<0.001. CI=confidence interval. SD=standard deviation.

Based on tolerability, 103 patients (82.4%) escalated and remained on dose of 3.0 mg, 11 patients (8.8%) escalated and remained on dose of 2.4 mg, 4 patients (3.2%) escalated and remained on dose of 1.8 mg, 4 patients (3.2%) escalated and remained on dose of 1.2 mg and 3 patients (2.4%) remained on dose of 0.6 mg.
No effects on growth or pubertal development were found after 56 weeks of treatment.

5.2 Pharmacokinetic properties

Absorption

The absorption of liraglutide following subcutaneous administration was slow, reaching maximum concentration approximately 11 hours post dosing. The average liraglutide steady state concentration ($AUC_{\tau/24}$) reached approximately 31 nmol/L in obese (BMI 30–40 kg/m^2) patients following administration of 3 mg liraglutide. Liraglutide exposure increased proportionally with dose. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution

The mean apparent volume of distribution after subcutaneous administration is 20–25 L (for a person weighing approximately 100 kg). Liraglutide is extensively bound to plasma protein (>98%).

Biotransformation

During 24 hours following administration of a single [^{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).

Elimination

Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as major route of 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 liraglutide is approximately 0.9–1.4 L/h with an elimination half-life of approximately 13 hours.

Special populations

Elderly

Age had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results from a population pharmacokinetic analysis of data from overweight and obese patients (18 to 82 years). No dosage adjustment is required based on age.