Risk Management Plan

Liraglutide in T2D and weight management

Active substance(s)	**Liraglutide**
RMP version number:	34.1
Data lock point for this RMP	31 Mar 2024
Date of final sign off:	See signature page
Rationale for submitting an updated RMP	Submission in connection with the Type II variation application for indication extension of liraglutide in weight management (Saxenda®) for children with obesity aged 6 to <12 years in the European Economic Area.
Summary of significant changes in this RMP	The RMP has been updated to include the following data pertaining to liraglutide in weight management (Saxenda®) • The proposed indication for liraglutide in weight management for children aged 6 to <12 years. • Data from the completed paediatric study NN8022-4392. • Data from post-marketing sources (including exposure) and epidemiology updates pertaining to overweight and obesity as of the DLP. • Update of various references and minor editorial changes have been made throughout the RMP. • Information on off-label use was deleted as removal of missing information 'off-label use' from the list of RMP safety concerns was endorsed by EMA (EMEA/H/C/003780/II/0034).
Other RMP versions under evaluation	None
Details of the currently approved RMP	Version number: 33.0 Approved with procedure: EMEA/H/C/003780/II/0034Date of approval (CHMP opinion): 01 Dec 2022
QPPV	Karsten Lollike
QPPV signature	See signature page

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Abbreviations

ADA	American Diabetes Association
AE	adverse event
ASCVD	atherosclerotic cardiovascular disease
ATC	anatomical therapeutic chemical
BMI	body mass index
CI	confidence interval
CKD	chronic kidney disease
CNS	central nervous system
CPRD	Clinical Practice Research Datalink
CSR	clinical study report
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
CYP	cytochrome P450
DLP	data lock point
DPP-4	dipeptidyl peptidase-4
DUS	drug utilisation study
EAC	Event Adjudication Committee
EASD	European Association for the Study of Diabetes
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European public assessment report
ESRD	end-stage renal disease
FDA	U.S. Food and Drug Administration
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GLP-1	glucagon-like peptide-1
GVP	Good Pharmacovigilance Practices
HbA_{1c}	glycated haemoglobin
HCP	healthcare professional
HHS	hyperosmolar hyperglycaemic state
IARC	International Agency for Research on Cancer
IFU	instructions for use
INN	international non-proprietary name
INR	international normalised ratio
IPSAD	International Society for Paediatric and Adolescent Diabetes
LADA	late onset autoimmune diabetes
MAA	marketing authorisation application
MACE	major adverse cardiac event
MAH	marketing authorisation holder
MASH	metabolic dysfunction-associated steatohepatitis
MASLD	metabolic dysfunction-associated steatotic liver disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	multiple endocrine neoplasia syndrome type 2
MetS	metabolic syndrome

MTC	medullary thyroid cancer
MW	molecular weight
NAACCR	North American Association of Central Cancer Registries
NASH	nonalcoholic steatohepatitis
NAFLD	nonalcoholic fatty liver disease
NCD	non-communicable diseases
NDA	new drug application
NDS	new drug submission
NEP	neutral endopeptidase
NIAD	non-insulin antidiabetic drug
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OAD	oral antidiabetic drug
ONS	Office for National Statistics
OR	odds ratio
OSA	obstructive sleep apnoea
PAES	post-authorisation efficacy study
PASS	post-authorisation safety study
PCOS	polycystic ovary syndrome
PD	pharmacodynamic(s)
PIL	patient information leaflet
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PSUR	periodic safety update report
PT	preferred term
PYE	patient/participant-years of exposure
PYO	patient-years of observation
QPPV	Qualified Person responsible for Pharmacovigilance
QRD	quality review of documents
RET	rearranged during transfection
RMP	risk management plan
RoW	Rest of the World
RR	reporting rate
s.c.	subcutaneous(-ly)
SAE	serious adverse event
SAR	serious adverse reaction
SCC	study coordinating centre
SGA	small for gestational age
SGLT2	sodium-glucose co-transporter 2
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA query
SOC	system organ class
SOP	standard operating procedure
SU	sulfonylurea
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus

TIA	transient ischaemic attack
TSH	thyroid stimulating hormone
UNL	upper normal limit
WHO	World Health Organization
WM	weight management

1 Products overview

This risk management plan concerns liraglutide indicated for the treatment of insufficiently controlled type 2 diabetes mellitus (Victoza®) and for weight management (Saxenda®).

Table 1-1 Product overview (Victoza® [Liraglutide in T2D] and Saxenda® [Liraglutide in weight management])

Active substance(s) (INN or common name)	Liraglutide
Pharmacotherapeutic group(s) (ATC Code)	Glucagon-like peptide (GLP-1) analogues; A10BJ02
Marketing authorisation holder	Novo Nordisk A/S DK-2880 Bagsværd Denmark
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Victoza® Saxenda®
Marketing authorisation procedure	EU: Centralised authorisation procedure
Brief description of the product	***Chemical class:*** Human glucagon-like peptide-1 (GLP-1) analogue ***Molecular formula*:** $C_{172}H_{265}N_{43}O_{51}$ (MW = 3,751.20)
	Summary of mode of action: Liraglutide acts as a GLP-1 receptor agonist (RA) that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological hormone with multiple actions in glucose and appetite regulation, and in the cardiovascular system. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain. Liraglutide works at pharmacological levels by lowering blood glucose and reducing body weight via a combination of effects described below. GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys from where it may mediate cardiovascular and microvascular effects. In addition to lowered systolic blood pressure, reduced selected inflammatory markers and increased heart rate seen in clinical studies, in individuals with T2D, liraglutide at doses up to 1.8 mg significantly reduced the risk of Major adverse cardiovascular events (MACE) versus placebo (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) and the risk of expanded MACE (primary MACE, unstable angina pectoris leading to hospitalisation, coronary revascularisation or hospitalisation due to heart failure) in the Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results (LEADER) trial. In individuals with overweight or obesity, liraglutide 3.0 mg provides a significant, clinically meaningful and sustained weight loss. 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.

	Composition: Human glucagon-like peptide-1 (GLP-1) analogue produced by recombinant DNA technology in *Saccharomyces cerevisiae*
Hyperlink to the Product Information:	Victoza® SmPC Saxenda® SmPC
Indication(s) in the EEA	***Current:*** **Victoza®** Victoza® 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 risk reduction, and the populations studied, see Sections 4.4, 4.5 and 5.1. **Saxenda®** *Adults:* Saxenda® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial body mass index (BMI) of: • ≥30 kg/m² (obese), or • ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea. Treatment with Saxenda® should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight. *Adolescents (≥ 12 years):* Saxenda® can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with: • obesity (BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points (IOTF)) and • body weight above 60 kg. Treatment with Saxenda® should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.
	Proposed: **Victoza®** Not applicable **Saxenda®** *Adolescents (≥ 12 years):* Saxenda® can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with: • obesity (BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points*) and • body weight above 60 kg.

	Treatment with Saxenda® should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose. *IOTF BMI cut-off points for obesity by sex between 12-18 years in accordance with study design of the Trail 4180 (see Section 5.1 of SmPC). *Children (6 years to <12 years)* Saxenda® is indicated as an adjunct to healthy nutrition and increased physical activity for weight management in children from the age of 6 to <12 years with: • obesity (BMI ≥ 95th percentile*) and • body weight ≥ 45 kg Treatment with Saxenda® should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose. *CDC BMI cut-off points for obesity (≥ 95th percentile) by sex between 6 to <12 years in accordance with study design of the Trial 4392 (see Section 5.1 of SmPC).
Dosage in the EEA	***Current:*** **Victoza®** To improve gastrointestinal tolerability, the starting dose is 0.6 mg liraglutide daily. After at least 1 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 1 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. Victoza® must not be administered intravenously or intramuscularly. Victoza® 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 Victoza® is injected around the same time of the day, when the most convenient time of the day has been chosen. 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 of the SmPC). **Saxenda®** The starting dose is 0.6 mg once daily. The dose should be increased to 3.0 mg once daily in increments of 0.6 mg with at least 1 week intervals to improve gastrointestinal tolerability. If escalation to the next dose step is not tolerated for two consecutive weeks, consider discontinuing treatment. Daily doses higher than 3.0 mg are not recommended. For adolescents and children aged 6 years and above, a similar dose escalation schedule as for adults should be applied. The dose should be increased until 3.0 mg (maintenance dose) or maximum tolerated dose has been reached. Daily doses higher than 3.0 mg are not recommended. The safety and efficacy of Saxenda® in children below 6 years of age has not been established (see section 5.1 of SmPC).

	Saxenda® is for subcutaneous use only. It must not be administered intravenously or intramuscularly. Saxenda® is administered once daily at any time, independent of meals. It should be injected in the abdomen, thigh or upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that Saxenda® is injected around the same time of the day, when the most convenient time of the day has been chosen.
	Proposed: **Victoza®** Not applicable **Saxenda®** Not applicable.
Pharmaceutical form(s) and strengths	**Current:** Solution for injection: Clear and colourless or almost colourless, isotonic solution; pH = 8.15. 1 mL of solution contains 6 mg of liraglutide. Each pre-filled pen contains 18 mg liraglutide in 3 mL.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	**Victoza®** No **Saxenda®** No

Abbreviations: BMI = body mass index; CV = cardiovascular; EEA = European Economic Area; GLP-1 = glucagon-like peptide-1; GLP-1R = GLP-1 receptor; IOTF = International Obesity Task Force; MACE = major adverse cardiovascular event; MW= molecular weight; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus.

2 Safety specification

2.1 Module SI: Epidemiology of the indication(s) and target population

2.1.1 Indication

Type 2 diabetes mellitus

Diabetes mellitus is a group of metabolic abnormalities characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.[1] T2D is a heterogeneous, chronic and progressive metabolic disease primarily characterised by abnormal glucose and lipid metabolism leading to chronic hyperglycaemia associated with insulin resistance, along with impaired insulin secretion due to relatively impaired beta-cell function. While the course of development of the disease is variable, it usually follows a predictable course of deteriorating β-cell function and increasing insulin resistance.

Overweight and obesity

The European Association for the Study of Obesity (EASO),[2] World Obesity Federation,[3] American Medical Association (AMA)[4] and a number of leading institutions[5-8] have classified obesity as a disease, calling for dedicated efforts in prevention, diagnosis and treatment. The World Health Organization (WHO) defines overweight as BMI ≥25 kg/m^2 and obesity as BMI ≥30 kg/m^2. Obesity is further divided into following classes:[9]

- Obesity class I equals a BMI between 30 kg/m^2 and <35 kg/m^2
- Obesity class II equals a BMI between 35 kg/m^2 and <40 kg/m^2
- Obesity class III equals a BMI of 40 kg/m^2 or higher

2.1.1.1 Incidence and prevalence

Incidence and prevalence of type 2 diabetes mellitus

The prevalence and incidence rates of type 2 diabetes mellitus (T2D) are rising rapidly throughout the world.[10-15] The growing burden of diabetes is driven mainly by the combined effects of increased ageing of the population, the improved survival of patients with T2D and the rising levels of obesity and inactivity.[16] The incidence rates of T2D in adults range from 2.3 to 20.2 cases per 1,000 person-years with wide geographical variation.[3, 5, 8, 10-22] In 2019, the estimated crude prevalence of diabetes in adults was 8.8% both globally and in Europe (the vast majority of cases are T2D). Estimated (crude) prevalence of diabetes in Europe was highest in Germany (15.3%) and Malta (12.2%), and the lowest (crude) European prevalence of diabetes has been reported in Greenland (3.2%), Ireland (4.4%) and Lithuania (5.4%).[17] For children and adolescents, the incidence and prevalence rates vary widely depending on age, sex, ethnicity and geographical region, with incidence rates ranging from 0 to 330 per 100,000 person–years and prevalence ranging from 0% to 5.1%.[18] The lowest incidence rates were observed in European countries; the Netherlands had no new cases of T2D during the period 1998-2000 and in Austria the incidence rate was 0.29 per 100,000 person-years for the 1999–2007 period.[18] The UK has the highest reported prevalence of T2D (9 per 100,000 15--19-year olds) in Europe.[18]

Incidence and prevalence – Overweight and obesity

In 2022, there were 2.5 billion adults (aged 18 years and above) with overweight constituting 43%of the world's adult population (43% of men and 44% of women). Of these, over 890 million adults had obesity constituting about 16% of the world's adult population . In adults, obesity rates nearly tripled among women (6.6% to 18.5%) and quadrupled in men (3.0% to 14.0%) between 1975 and 2022. In the same period, the prevalence of obesity among children and adolescent (5-19 years) has increased 10-fold; from 0.7% to 6.9% for girls and from 0.9% to 9.3% for boys.

According to a US forecast study, it is anticipated that by 2030, almost half (projected prevalence - 48.9%) of all adults will be living with obesity. Additionally, the study suggests that nearly a quarter (projected prevalence - 24.2%) of adults will be living with severe obesity. [22],[23-25]

2.1.1.2 Demographics of the target population – Age, gender, racial and ethnic origin

Type 2 diabetes mellitus

T2D usually occurs in adults but is increasingly seen in children and adolescents. The prevalence[11] and incidence[12] of T2D becomes progressively higher with advancing age. The incidence[12, 26-28] and prevalence[29] of T2D tend to be a little higher in men than in women. In the US, Whites have lower incidence[30] and prevalence[31] of T2D than other ethnic groups. The prevalence is highest in African Americans[31] and the incidence is highest in Pacific Islanders and South Asians.[30]

Overweight and obesity

Once considered a high-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in urban settings.[19] This is reflected in the increasing prevalence and incidence of T2DM (see Section 2.1.1.1).[32]

The prevalence of overweight and obesity in adults across WHO regions is presented in Table 2-1 and that in children and adolescents is presented in Table 2-2.

Table 2-1 Age-standardised prevalence of overweight (BMI ≥25 kg/m^2) and obesity (BMI ≥30 kg/m^2) in >20-year olds across WHO regions, 2022[33, 34]

Region	Overweight (%) BMI ≥25 kg/m^2		Obesity (%) BMI ≥30 kg/m^2	
	Males	Females	Males	Females
Global	43.1	43.9	13.2	17.5
Europe	61.9	49.9	22.3	22.7
Americas	67.3	67.6	30.9	36.4

Abbreviations: BMI = body mass index; WHO = World Health Organization.

Table 2-2 Obesity prevalence amongst children aged 5−19 years in 2020 and 2035, by WHO region[32]

Region	Children and adolescents (aged 5-19 years)			
	2020		2035	
	Male	Female	Male	Female
Global	10%	8%	20%	18%
Europe	13%	8%	21%	14%
Americas	20%	16%	33%	26%

Abbreviations: WHO = World Health Organization.

2.1.1.3 Risk factors for the disease

Risk factors for the disease – Type 2 diabetes mellitus

Although the exact causes for the development of T2D are still not known, there are several important risk factors. The most important are excess body weight (overweight and obesity), physical inactivity, dietary factors and genetics.[11] Additional risk factors include smoking, impaired glucose tolerance, abnormal lipids, hypertension, inflammation, intrauterine environment, age, sex, ethnicity, history of gestational diabetes and polycystic ovary syndrome.

Risk factors for the disease – Overweight and obesity

The scientific understanding of the pathophysiology of obesity has advanced, and it is now viewed as a complex chronic disease with interacting genetic, environmental and biological determinants.[35]

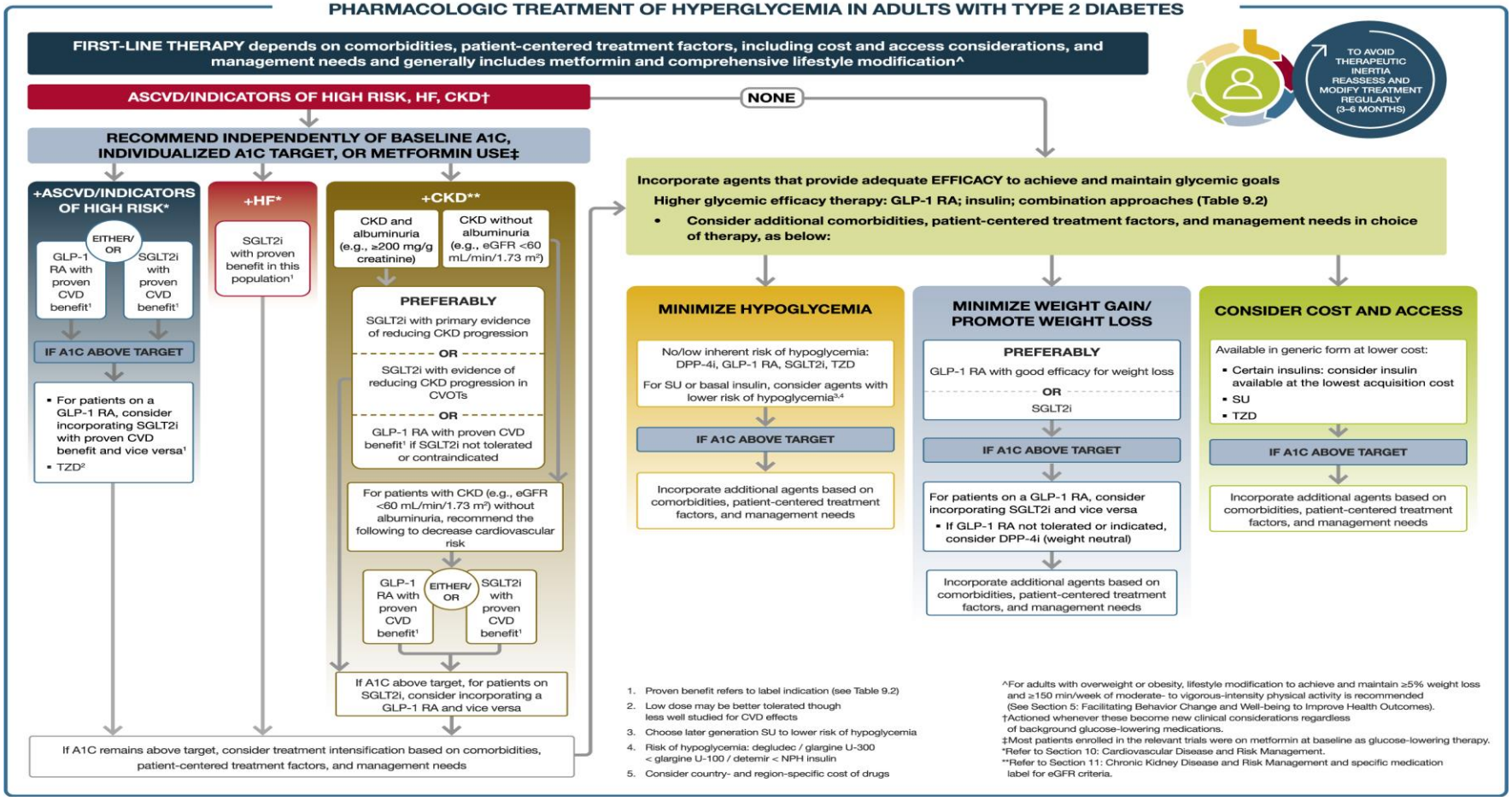
Most cases of childhood obesity also arise from interactions between genetic factors that enhance susceptibility and environmental factors that increase food intake and decrease energy expenditure, specifically those related to a sedentary lifestyle and unfavourable eating patterns.[36, 37]

2.1.1.4 The main existing treatment options

Type 2 diabetes mellitus

The European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) consensus report on the management of hyperglycaemia in patients with T2D and the ADA guideline recommend to start with metformin in combination with comprehensive lifestyle modifications (Figure 2-1). [38, 39] Management of hyperglycaemia in T2D should have a patient-centred approach, and should take into account the patient's clinical conditions (i.e., ASCVD, heart failure and CKD), clinical characteristics (i.e., age, HbA1c and weight), factors related to the pharmacological treatment (risk of hypoglycaemia, side effects, effects on body weight) and the cultural and socioeconomic context. It should also ensure that patient values guide all clinical decisions in the shared decision-making process, regarding both the intensiveness of blood glucose control and which medications are selected.[38, 40, 41]

Figure 2-1 Glucose-lowering medication in type 2 diabetes: overall approach



Note: Pharmacologic treatment of hyperglycemia in adults with type 2 diabetes. 2022 ADA Professional Practice Committee (PPC) adaptation of Davies et al.[42] and Buse et al.[39]. The 2022 ADA PPC adaptation emphasizes incorporation of therapy rather than sequential add-on, which may require adjustment of current therapies. Therapeutic regimen should be tailored to comorbidities, patient-centered treatment factors, and management needs.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; CVOTs = cardiovascular outcomes studies; DPP-4i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide 1 receptor agonist; HF = heart failure; NPH = Neutral Protamine Hagedorn insulin; SGLT2i = sodium–glucose cotransporter 2 inhibitor; SU = sulfonylurea; T2D = type 2 diabetes; TZD = thiazolidinedione.

Paediatric population with T2D

The main treatment options for T2D in children, according to International Society for Paediatric and Adolescent Diabetes (IPSAD) guidelines, include lifestyle modification, pharmacologic treatment initially with metformin and insulin alone or in combination (depending on degree of hyperglycaemia and metabolic disturbances, and presence or absence of ketosis/ketoacidosis) to normalise glycaemia (HbA_{1c} of <7%) as well as regular self-monitored blood glucose.[43] Similar glycaemic targets and pharmacologic management are recommended by the ADA.[44]

Overweight and obesity

Weight loss is advised to lower the risk of obesity-related complications, even a modest weight loss of 5-10% from the initial weight has been linked to significant improvements in cardiovascular disease risk factors. A weight reduction of 1-4.9% has also been shown to reduce the risk of non-alcoholic fatty liver disease (NAFLD)/ metabolic dysfunction–associated steatotic liver disease (MASLD) and non-alcoholic steatohepatitis (NASH)/ metabolic dysfunction-associated steatohepatitis (MASH). For individuals with obesity, a substantial weight loss of 10% or more can significantly improve the conditions or the risk of other obesity-related complications such as T2D, hypertension, cancer, knee osteoarthritis, sleep apnoea, fertility, and overall quality of life. [53-55]

Main treatment options for obesity include:[54, 55]

- non-surgical and non-pharmacotherapeutical treatment options, including lifestyle modifications (diet and exercise) and psychological support
- pharmacological treatment
- bariatric surgery.

Lifestyle intervention in the form of dietary and behavioural change is the mainstay in obesity management. There is evidence that the effect of the lifestyle modifications can be enhanced through behavioural and cognitive-behavioural strategies.[56] However, data indicate that weight loss through lifestyle interventions is on average modest and that more than 50% of the patients who lose weight through lifestyle modifications return to their baseline weight within 5 years.[57]

At the other end of the treatment spectrum lies bariatric (weight loss) surgery, which is currently the most effective approach providing significant weight loss and long-term weight loss maintenance for people with severe obesity (BMI ≥40 kg/m^2).[58]

In between lifestyle intervention and surgery is pharmacological intervention. In Europe, there are currently 4 marketed products licensed for the long-term treatment of obesity: these are orlistat (Xenical®), naltrexone/bupropion (Mysimba®), liraglutide (Saxenda®) and semaglutide (Wegovy®).

Paediatric population with obesity

Paediatric obesity remains a major public health challenge as treatment options are limited. Although lifestyle modification is the recommended first-line treatment, widespread adoption of this treatment method and long-term compliance are problematic.[59-61] The U.S Food and Drug Administration (FDA) and the European Medicines Agency (EMA) has approved a limited amount of medications for weight management in adolescents aged 12 years or older including liraglutide

and semaglutide. No medication is currently approved for the treatment of general obesity in paediatric population <12 years of age.

2.1.1.5 Natural history of the indicated condition including mortality and morbidity

Type 2 diabetes mellitus

T2D is a heterogeneous, chronic and progressive disease characterised by insulin resistance, along with relatively impaired beta-cell function. While the course of the disease is variable, it usually follows a predictable course. In the early stages, individuals with T2D have sufficient pancreatic reserves to compensate for insulin resistance and can maintain relatively normal blood glucose levels. However, over time, this ability to compensate decreases as beta-cells gradually lose their ability to secrete insulin (beta-cell insufficiency), and may eventually lead to a state of insulin dependency.[62]

The endpoint of the disease process, insulin deficiency, can be absolute or relative in the coexistence of insulin resistance (response to insulin to the target tissues, such as muscle, liver and adipose tissue). The result is chronic hyperglycaemia, caused by reduced insulin secretion, decreased insulin utilisation and increased liver glucose production, which in the long run leads to diabetic complications. Diabetes is a leading cause of end-stage renal disease (ESRD), non-traumatic lower extremity amputations, adult blindness and cardiovascular complications.[16, 62, 63]

T2D is associated with increased all-cause mortality;[46] cardiovascular mortality (including death following heart failure[64] and myocardial infarction[65-67]) is increased and may account for 50% or more of deaths due to diabetes in some populations.[11] Cancer patients with diabetes have poorer survival and higher cancer mortality rates than cancer patients without diabetes[68, 69] particularly so for liver, pancreatic, ovarian and colorectal cancer.[70]

Overweight and obesity

Obesity is a chronic condition associated with a 5–10 years decreased life expectancy, as well as several major comorbidities/complications, including hypertension, dysglycaemia (pre-diabetes and diabetes), dyslipidaemia, NAFLD/MASLD, gastro-oesophageal reflux disease, acute pancreatitis, coronary artery disease, stroke, polycystic ovary syndrome, infertility, adverse pregnancy outcomes, obstructive sleep apnoea, atherosclerosis, malignant neoplasms, gallbladder disease, osteoarthritis, hypothyroidism and depression.[71] The WHO has estimated that the burden of disease (defined as mortality and loss of health due to disease) that can be attributed to overweight or obesity is 44% for diabetes, 23% for ischaemic heart disease and 7–41% for certain cancer types. [72] In 2019, around 5 million deaths worldwide could be attributed high BMI (BMI ≥25).

Increasing BMI is associated with increased risk of all-cause mortality. A large meta-analysis of more than 200 prospective studies showed increasing risk of all-cause mortality with increasing BMI category compared to normal weight individuals. Individuals with obesity grade 1, grade 2 and grade 3 have 45%, 94% and 176% higher risk of all-cause mortality, respectively, compared to normal weight individuals.[73]

2.1.1.6 Important co-morbidities found in the target population

Type 2 diabetes mellitus

People with diabetes are at higher risk of developing a number of disabling and life-threatening health problems than people without diabetes.[11] Persistent hyperglycaemia may lead to development of microvascular pathology in the retina, renal glomerulus and peripheral nerve.[74] As a consequence of its microvascular pathology, diabetes is a leading cause of blindness, ESRD and a variety of debilitating neuropathies. Diabetes is also associated with accelerated atherosclerotic macrovascular disease affecting arteries that supply blood to the heart, brain and lower extremities. As a result, individuals with diabetes have a much higher risk of myocardial infarction, stroke and limb amputation.

An overview of the important co-morbidities/complications found in the target population is shown in Table 2-3.

Table 2-3 Important co-morbidities/complications in the target population – T2D

Disorders	Important co-morbidities/complications
Microvascular disorders	Neuropathy, chronic kidney disease and nephropathy, retinopathy and foot ulcers
Macrovascular disorders	Congestive heart failure, myocardial infarction, peripheral arterial disease and stroke
Acute complications	Ketoacidosis, hyperosmolar hyperglycaemic state (HHS)
Other disorders and complications	Metabolic syndrome or any of its components (including dyslipidaemia, hypertension, central obesity), pancreatitis and several types of cancers (liver, pancreas, colorectal and breast)

Abbreviations: T2D = type 2 diabetes mellitus.

Overweight and obesity

Overweight and obesity are defined as an abnormal or excessive fat accumulation that may impair health.[75] Obesity is associated with multiple medical complications that lead to increased morbidity and reduced life expectancy. These complications include CVDs, T2D, NAFLD/MASLD, metabolic syndrome, cholelithiasis, hypertension, cancer, sleep apnoea, osteoarthritis and reduced psychosocial function.[76] The most serious or common co-morbidities/complications are presented in Table 2-4.

Paediatric obesity is associated with a number of complications, including hypertension, T2D, early puberty, menstrual irregularities and PCOS (in girls), steatohepatitis, sleep apnoea, asthma, musculoskeletal disorders and psychological problems.[77] Childhood and adolescent obesity not only impacts the immediate health of young individuals but also increases the likelihood and earlier onset of numerous non-communicable diseases (NCDs) like type 2 diabetes and cardiovascular issues. Childhood and adolescent obesity can also lead to negative psychosocial effects, affecting academic performance and overall well-being due to associated stigma, discrimination, and bullying. Furthermore, children with obesity are more likely to carry this condition into adulthood, thereby increasing their risk of NCDs later in life.

Table 2-4 Important co-morbidities/complications in the target population – Overweight and obesity

Disorders	Important co-morbidities/complications
Metabolic disorders	Metabolic syndrome or any of its components (including dyslipidaemia, hypertension, central obesity), NAFLD/MASLD, prediabetes and type 2 diabetes
Gastrointestinal disorders	Gastro-oesophageal reflux disease (GERD), acute pancreatitis
Cardiovascular disorders	Hypertension, coronary artery disease (CAD), stroke
Reproductive disorders	Polycystic ovary syndrome (PCOS), infertility, adverse pregnancy outcomes
Other disorders and complications	Malignant neoplasms, gallbladder disease, osteoarthritis, hypothyroidism, obstructive sleep apnoea (OSA) and depression

Abbreviations: CAD = coronary artery disease; GERD = Gastro-oesophageal reflux disease; MASLD = metabolic dysfunction–associated steatotic liver disease; NAFLD = non-alcoholic fatty liver disease; OSA = obstructive sleep apnoea; PCOS = polycystic ovary syndrome.

2.2 Module SII: Non-clinical safety findings

2.2.1 Important nonclinical safety findings and their relevance to human use

Table 2-5 Important nonclinical safety findings and their relevance to human use

Key safety findings (from nonclinical studies)	Relevance to human usage
Toxicity • **Reproductive and developmental toxicity** Reduced maternal food consumption and no overall body weight gain were observed in rats and rabbits at all dose levels, which are considered to be part of the expected pharmacological effect. Studies in animals have shown reproductive toxicity. At the 2 highest maternal dose levels in rabbits (0.025 mg/kg/day and 0.05 mg/kg/day), the incidence of offspring with supernumerary ribs was significantly higher than that in the controls. Furthermore, in rabbits, the induction of supernumerary ribs has been attributed to maternal stress, including food deprivation.[78, 79] In rabbits, there was an increased incidence of fetuses with jugals connected to or fused to maxilla in the highest dose group (0.05 mg/kg). The incidence of jugals fused to the maxilla was slightly above the historical control range observed at the performing laboratory. The connections/fusions were classified as minor skeletal variations. In rats, a slight increase in early embryonic death, as well as an increased incidence of minimally kinked ribs, was seen at 1 mg/kg/day. The effects observed in the reproductive toxicity investigations revealed changes that can possibly be ascribed to maternal reduced food intake or maternal stress.	**Toxicity** • **Reproductive and developmental toxicity** Weight loss in pregnant women is reported to cause reduced neonatal birth weights, placental weights and umbilical cord length compared to controls, adjusted for BMI ($p < 0.05$). Preterm delivery and small for gestational age (SGA) infants were more frequently observed in women with gestational weight loss compared with controls (odds ratio [OR]: 6.3; 95% confidence interval [CI]: 3.3, 12.1, OR: 4.3; $[1.9; 9.9]_{95\% CI}$. Preterm premature rupture of membrane was observed in 10.8% of the women with gestational weight loss and 1.8% of the controls (OR: 6.6; $[1.7; 25.1]_{95\% CI}$). However, the frequencies of chorioamnionitis and the cervical length at second trimester were not different between the 2 groups.[80] Hence, liraglutide should not be used during pregnancy.
Juvenile animals Subcutaneous administration of liraglutide to juvenile rats for 10 weeks produced adverse signs of toxicity among females at a dose level of 0.25 mg/kg/day and above, resulting in a marked delay in the attainment of sexual maturation at 0.25 mg/kg/day and 1 mg/kg/day. Males were lesser affected than females. Ovary weights were slightly reduced at treatment end but normal after a 4-week off-drug recovery period. Following mating after a 4-week off-drug period, slightly low implantation counts and post-partum litter size were noted in females previously dosed at 1 mg/kg/day, for which a relationship to treatment could not be discounted. There were no toxicologically significant changes observed among liraglutide-treated males. Food restriction during early postnatal development is well known to delay sexual maturation and reduce ovarian weight in rats.[81-83]	**Paediatric population** The finding is considered relevant for pre-pubertal children where sexual maturation is influenced by body weight and body fat mass, particularly in females.[84] If treatment with liraglutide is initiated before onset of puberty, a delay in puberty cannot be excluded.

Key safety findings (from nonclinical studies)	Relevance to human usage
Carcinogenicity Non-lethal thyroid C-cell tumours were seen in 2-year carcinogenicity studies in rats and mice. 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.	**Carcinogenicity** Published data indicate that the GLP-1 receptor is not expressed in the normal human thyroid C-cells.[85, 86, 87] Based on available data for GLP-1 RAs, the human relevance of the rodent C-cell tumours is considered to be low.
General safety pharmacology • **Increased heart rate and blood pressure in rats** Liraglutide at 0.2 mg/kg and 2.0 mg/kg induced a dose-related increase in blood pressures and heart rate, which was generally maintained for up to 24 hours after dosing. The cardiovascular effect observed in rats is likely mediated through the GLP-1 receptor since native GLP-1 or other GLP-1 analogues cause pronounced hypertension and chronotropy in rats when injected intravenously or in the ventricles of the brain. Mesenteric and renal vasoconstriction is probably responsible for the blood pressure increase.[88-93] • **Increased diuresis and electrolyte excretion in rats** A dose-related diuretic effect has been seen in rodents. The diuretic effects disappear after chronic administration and no renal effects were seen in repeat-dose toxicity studies in rats and non-human primates (cynomolgus monkey). GLP-1-receptor-agonist-induced increased diuresis in rats is well known.[94]	**General safety pharmacology** • **Increased heart rate and blood pressure in rats** The cardiovascular observation in rat is not representative for humans, where liraglutide decreases blood pressure in long-term clinical studies, with a concomitant small increase in heart rate (by 2–3 beats per minute). • **Increased diuresis and electrolyte excretion in rats** Increased diuresis/natriuresis after single dosing of liraglutide in rats is a specific rat phenomenon well known for GLP-1 analogues. This response is not thought to be relevant for human usage.
Mechanisms for drug interactions *In vitro*, liraglutide has shown very low potential to be involved in pharmacokinetic interactions with other active substances related to cytochrome P450 (CYP) and plasma protein binding.	**Mechanisms for drug interactions** No evidence for impact on clinical use by drug interactions via CYP-mediated metabolism or plasma protein binding. The small delay of gastric emptying with liraglutide may influence absorption of concomitantly administered oral medicinal products.
Other toxicity-related information or data • **Local irritation** The injection site reactions observed in animals after single or repeated s.c. dosing were generally minimal to mild. Injection site reactions in nonclinical, long-term repeat-dose toxicity studies generally increased in severity because the injections were given in a small area. Following intra-arterial injection of liraglutide to rabbits, slight to moderate haemorrhage, erythema and swelling at the injection site were observed.	**Other toxicity-related information or data** • **Local irritation** Based on their limited nature, all findings following s.c., i.m., i.v. and i.a. administration of liraglutide in the marketed formulation were considered of no concern to human safety.

Key safety findings (from nonclinical studies)	Relevance to human usage
• **Immunogenicity** In the 52-week repeat-dose toxicity study in cynomolgus monkeys, liraglutide antibodies developed in 3 animals from the high-dose group. The antibody-positive samples were identified after 52 weeks of treatment or at the end of the recovery period (a recovery period was only included at the highest dose level). Some cross-reactivity was seen to natural GLP-1. The presence of antibodies had apparently no effect on the pharmacological effect of liraglutide.	• **Immunogenicity** The nonclinical studies demonstrated a low immunogenic potential for liraglutide in animals; however, nonclinical studies are not predictive for human immunogenicity.

Abbreviations: BMI = body mass index; CI = confidence interval; CYP = cytochrome P450; GLP-1 = glucagon-like peptide-1; i.a. = intra-arterial; i.m. = intramuscular; i.v. = intravenous; OR = odds ratio; RMP = risk management plan; s.c. = subcutaneous(-ly); SGA = small for gestational age.

2.2.2 Conclusions on nonclinical data

Table 2-6 Nonclinical summary of safety concerns

Safety concerns
Important identified risks (confirmed by clinical data) • None
Important potential risks (not refuted by clinical data or which are of unknown significance) • Medullary thyroid cancer (C-cell carcinogenicity)
Missing information • None

2.3 Module SIII: Clinical study exposure

Liraglutide has been investigated in three indications. A short description of the clinical development programme for the different indications is presented below followed by exposure to liraglutide by dose, duration, age and race for the 2 approved indications: T2D and WM.

Liraglutide in T2D: The first clinical study for liraglutide was conducted in the period 25 Mar 1999-20 Dec 1999 (study NN2211-1149). In addition to the glycaemic control studies identified by the project number NN2211, a cardiovascular outcome study (CVOT) EX2211-3748 [The Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results (LEADER)] was conducted with liraglutide.

Liraglutide in WM: The clinical study programme for liraglutide in weight management was initiated in 2007. Clinical studies conducted with liraglutide in weight management are identified by the project name NN8022. Exposure in the paediatric studies NN8022-4180 and NN8022 4392 are presented separately in Section 2.3.1 and 2.3.2 by duration, age range, gender and race. The exposure from these paediatric studies is also included in the cumulative exposure (Section 2.3.3).

Type 1 diabetes mellitus: Previously, liraglutide had been investigated as an adjunct to insulin in patients with T1D (project name NN9211). The safety profile was generally consistent with the established profile in participants with T2D.

Based on a risk–benefit assessment of the overall dataset from the two ADJUNCT clinical studies (NN9211-3919 and NN9211-4083), Novo Nordisk decided not to submit an application to expand the label of liraglutide for use in T1D. The results of these two studies have been published and no new safety concerns were identified with liraglutide.[95, 96]

2.3.1 Exposure from the completed paediatric study with liraglutide in WM, NN8022-4180

This was a 56-week, randomised, double-blind, parallel-group, placebo-controlled, multi-national study followed by a 26-week off-study-drug period, conducted to evaluate the efficacy and safety of liraglutide in adolescent participants aged 12 to less than 18 years, with obesity. Participants were randomised 1:1 to receive either liraglutide or placebo as once-daily s.c. injection. The 26-week off-study-drug follow-up period was considered to be sufficient to assess effect maintenance, any evidence of weight regain and to monitor post-treatment safety.

Table 2-7 shows the total exposure to liraglutide and placebo in the paediatric study, NN8022-4180. The majority of the participants escalated and remained on the 3.0 mg dose through the treatment period; see Table 2-8. The mean duration of exposure was approximately 52 weeks in both the liraglutide 3.0 mg group and placebo group during the on-treatment period (for details, see Table 2-9). The majority of the participants were females (>50%) and of White origin (>80%) in both the treatment groups (Table 2-10 and Table 2-11, respectively).

Table 2-7 Exposure to liraglutide and placebo by treatment, in the study NN8022-4180

Population	Liraglutide N	Liraglutide PYE	Placebo N	Placebo PYE
WM	125	120.8	126	120.1

N: Number of participants.
PYE: Participant years of exposure.
Cumulative reporting period ending 31 Oct 2019.
WM: Weight management.
PYE: participant-years of exposure is calculated as the time from first drug date to last drug date plus 1 day.

Table 2-8 Exposure to liraglutide and placebo by dose, in the study NN8022-4180

Dose	Lira 3.0 mg n	Lira 3.0 mg (%)	Lira 3.0 mg Median (%)	Placebo n	Placebo (%)	Placebo Median (%)
Number of participants	125			126		
0.6 mg	3	(2.4)	62.5	0		
1.2 mg	4	(3.2)	68.6	1	(0.8)	29.4
1.8 mg	4	(3.2)	86.0	1	(0.8)	14.3
2.4 mg	11	(8.8)	87.2	0		
3.0 mg	103	(82.4)	92.8	124	(98.4)	92.8

n: Number of participants; %: Percentage of participants, Median (%): Median percentage of time on each dose.

Table 2-9 Exposure to liraglutide and placebo by duration, in the study NN8022-4180

Population	Duration (months)	Liraglutide N	Placebo N
WM	>0 months	125	126
	>1 month	122	126
	>2 months	122	124
	>3 months	119	122
	>4 months	116	118
	>5 months	116	115
	>6 months	113	112
	>7 months	110	107
	>8 months	109	106
	>9 months	108	103
	>10 months	106	102
	>11 months	103	100
	>12 months	102	100
	>13 months	15	20

N: Number of participants.
Cumulative reporting period ending 31 Oct 2019.
WM: Weight management.

Table 2-10 Exposure to liraglutide and placebo by age range and gender, in the study NN8022-4180

		Liraglutide			Placebo		
Population	Age range	Male N (PYE)	Female N (PYE)	Total N (PYE)	Male N (PYE)	Female N (PYE)	Total N (PYE)
WM	Adolescents 12-17 years	54 (54.6)	71 (66.2)	125 (120.8)	48 (46.3)	78 (73.8)	126 (120.1)

N: Number of participants, PYE: Participant years of exposure.
Cumulative reporting period ending 31 Oct 2019.
WM: Weight management.
PYE: participant-years of exposure is calculated as the time from first drug date to last drug date plus 1 day.

Table 2-11 Exposure to liraglutide and placebo by racial group, in the study NN8022-4180

		Liraglutide		Placebo	
Population	Racial group	N	PYE	N	PYE
WM	AMERICAN INDIAN OR ALASKA NATIVE	0	0	1	0.6
	ASIAN	2	2.2	0	0
	BLACK OR AFRICAN AMERICAN	14	11.8	6	6.4
	WHITE	105	103.4	115	110.0
	OTHER	4	3.4	4	3.2
	Total	125	120.8	126	120.1

N: Number of participants.
PYE: Participant years of exposure.
Cumulative reporting period ending 31 Oct 2019.
WM: Weight management.
PYE: participant-years of exposure is calculated as the time from first drug date to last drug date plus 1 day.

2.3.2 Exposure from the completed paediatric study with liraglutide in WM, NN8022-4392

This was a double-blind, randomised, parallel group, placebo-controlled, multi-national clinical study comparing liraglutide 3.0 mg s.c. once daily with placebo in children, aged 6 to <12 years, with obesity with or without comorbidities. The main phase of the studywas completed, which included a 2-week screening, 12-week run-in and a 56-week treatment period with an off-drug follow-up period of 26-weeks. The extension phase is ongoing and involved an open-label treatment period with a 2-week screening, a 56-week treatment period, and a 2-week off-drug follow-up period, followed by a safety, follow-up phase with yearly visits for 2 years. This study design also provided long-term effect and safety data from the off-treatment, follow up period with yearly safety visits for 2 years after liraglutide 3.0 mg treatment discontinuation. This clinical study was also conducted to fulfil the regulatory requirement for paediatric studies from the FDA and the European Paediatric Committee (PDCO) of the European Medicines Agency (EMA).

Total exposure to liraglutide and placebo in the paediatric study, NN8022-4180 is presented in Table 2-12. Participants were randomised 2:1 to receive liraglutide 3.0 mg (with dose escalation) or placebo once daily through the treatment period; see Table 2-13. For duration of exposure in the liraglutide 3.0 mg group or the placebo group during the on-treatment period, see Table 2-14. The

majority of the participants were male (~54%) and of white origin (~72%), see Table 2-15 and Table 2-16, respectively.

Table 2-12 Exposure to liraglutide and placebo by treatment, in the study NN8022 4392

Population	Liraglutide N	Liraglutide PYE	Placebo N	Placebo PYE
WM	56	52.7	26	25.8

N: Number of participants.
PYE: Participant years of exposure.
Cumulative reporting period ending 31 Mar 2024.
WM: Weight Management.
PYE: participant-years of exposure is calculated as the time from first drug date to last drug date plus 1 day.

Table 2-13 Exposure to liraglutide and placebo by dose, in the study NN8022 4392

Dose	Lira 3.0 mg N	(%)	Median (%)	Placebo N	(%)	Median (%)
Number of participants	56			26		
0.3	0			0		
0.6	0			0		
1.2	3	(5.4)	75.0	0		
1.8	1	(1.8)	48.0	1	(3.8)	15.6
2.4	2	(3.6)	75.2	0		
3.0	50	(89.3)	88.8	25	(96.2)	92.2

N: Number of participants; %: Percentage of participants, Median (%): Median percentage of time on each dose.
Cumulative reporting period ending 31 Mar 2024.
WM: Weight Management.

Table 2-14 Exposure to liraglutide and placebo by duration, in the study NN8022 4392

Population	Duration (months)	Liraglutide N	Placebo N
WM	>0 months	56	26
	>1 month	54	26
	>2 months	52	26
	>3 months	52	24
	>4 months	49	24
	>5 months	49	24
	>6 months	49	24
	>7 months	49	24
	>8 months	48	24
	>9 months	47	24
	>10 months	47	23
	>11 months	46	23
	>12 months	45	22
	>13 months	8	5

N: Number of participants.
Cumulative reporting period ending 31 Mar 2024.
WM: Weight Management.

Table 2-15 Exposure to liraglutide and placebo by age range and gender, in the study NN8022 4392

		Liraglutide			Placebo		
Population	Age range	Male N (PYE)	Female N (PYE)	Total N (PYE)	Male N (PYE)	Female N (PYE)	Total N (PYE)
WM	Children	26	25	51	13	11	24
	2-11 yrs	(25.5)	(22.8)	(48.3)	(13.8)	(9.8)	(23.7)
	Adolescents	4	1	5	1	1	2
	12-17 years	(3.3)	(1.1)	(4.4)	(1.1)	(1.1)	(2.1)

N: Number of participants, PYE: Participant years of exposure.
Cumulative reporting period ending 31 Mar 2024.
WM: Weight Management.

Table 2-16 Exposure to liraglutide and placebo by racial group, in the study NN8022 4392

		Liraglutide		Placebo	
Population	Racial group	N	PYE	N	PYE
WM	AMERICAN INDIAN OR ALASKA NATIVE	1	1.1	0	0
	ASIAN	6	6.5	2	2.2
	BLACK OR AFRICAN AMERICAN	4	2.4	2	1.3
	WHITE	37	34.2	22	22.4
	OTHER	8	8.6	0	0
	Total	56	52.7	26	25.8

N: N: Number of participants
PYE: Participant years of exposure.
Cumulative reporting period ending 31 Mar 2024.
WM: Weight Management.

2.3.3 Cumulative exposure

Cumulatively, up until 31 Mar 2024, a total of 15,750 participants were exposed to liraglutide (compared to 8,147 participants exposed to placebo or active comparator) in completed Novo Nordisk-sponsored clinical studies in which liraglutide was used as the investigational drug (excluding the CVOT EX2211-3748 [LEADER]); see Table 2-17.

Exposure in the CVOT EX2211-3748 (LEADER) is not included in the pool of NN2211, NN8022 and NN9211 clinical studies due to the nature of the study study design and the population studied (see Section 2.3.3.1 for details). In the CVOT EX211-3748, a total of 4,668 participants were exposed to liraglutide and 4,672 participants were exposed to placebo (see Table 2-18).

Table 2-17 Total cumulative exposure to liraglutide and comparators in completed clinical studies by population/indication and treatment (excluding the CVOT EX2211−3748 LEADER)

studiesstudies

Population	Treatment	Number of participants (%)	PYE
Liraglutide in all indications			
Healthy Participants	Liraglutide	531 (89.2)	17.2
	Active Comparator	24 (4.0)	0.3
	Placebo	204 (34.3)	12.4
	Total	595 (100.0)	29.9
T2DM	Liraglutide	8924 (69.5)	6476.2
	Active Comparator	2553 (19.9)	1723.2
	Placebo	1820 (14.2)	826.0
	Total	12846 (100.0)	9025.5
WM	Liraglutide	4579 (64.6)	6050.3
	Active Comparator	95 (1.3)	121.8
	Placebo	2854 (40.3)	3017.5
	Total	7085 (100.0)	9189.6
T1DM	Liraglutide	1716 (75.5)	1156.4
	Placebo	597 (26.3)	394.8
	Total	2273 (100.0)	1551.1
All Participants	Liraglutide	15750 (69.1)	13700.1
	Active Comparator	2672 (11.7)	1845.3
	Placebo	5475 (24.0)	4250.7
	Total	22799 (100.0)	19796.1

PYE: Participant-years of exposure is calculated as the time from first drug date to last drug date plus 1 day, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus,WM: weight management.
Cumulative reporting period ending 31 Mar 2024.
Clinical pharmacology studies included: NN2211-1149, 1189, 1219, 1224, 1326, 1327, 1328, 1329, 1330, 1331, 1464, 1551, 1589, 1591, 1608, 1636, 1644, 1692, 1693, 1694, 1698, 1699, 1745, 1800, 2063, 3533, 3534, 3673, NN8022-3630, 3967, 4162, 4181, 4192, NN9211-3953.
Exploratory or confirmatory studies included: NN2211-1310, 1332, 1333, 1334, 1436, 1499, 1571, 1572, 1573 (including extension 3529 study), 1574, 1697, 1700, 1701, 1796, 1797, 1799, 1842, 1860, 2072, 3619, 3659,3867, 3916, 3917, 3924, 3925, 3987, 4059, 4075, 4174, 4315, NN8022-1807, 1807-ext1, 1807-ext2, 1839 (1-year and 3-year data), 1922, 1923, 3970, 4180, 4272, 4274, 4392, NN9211-3919, 4083.
Active comparators: Oral anti-diabetics, Exenatide, Glargine, Glibenclamide, Glimepiride Insulin Degludec, Lixisenatide, Sitagliptine, Sulphonylurea
In cases where participants changed treatment arms, the percentage of participants does not add to 100.

Exposure in clinical pharmacology studies constitutes only approximately 6% of the total exposure for ‘liraglutide in T2D’ and 4.4% of the total exposure for ‘liraglutide in WM’. Considering the extensive exposure in exploratory/confirmatory studies, exposure presented in Sections 2.3.3.1 and 2.3.3.2 includes only these studies and does not include exposure from clinical pharmacology studies.

2.3.3.1 Liraglutide in T2D

LEADER study (CVOT EX2211-3748)

Table 2-18 to Table 2-20 show exposure and observation time to liraglutide in the LEADER study (EX2211-3748) conducted in patients with T2D and at a high risk of cardiovascular events. The primary objective of the study was to determine the long-term effect of liraglutide on cardiovascular outcomes in participants with T2D at high risk of cardiovascular events. The duration of the study for each participant was at least 3.5 years and up to 5 years.

A total of 4,668 participants were exposed to liraglutide in this study (compared to 4,672 participants exposed to placebo). The majority of the participants exposed in both the treatment groups were males and adults aged between 18 and 64 years (Table 2-20). Most of the participants escalated to the highest dose of 1.8 mg of liraglutide (Table 2-19).

Table 2-18 Observation time by treatment – LEADER trial

	Lira	Placebo	Total
Number of participants	4668	4672	9340
Randomised, N (%)			
N	4668 (100.0)	4672 (100.0)	9340 (100.0)
0- 1 Years	67 (1.4)	68 (1.5)	135 (1.4)
1- 2 Years	92 (2.0)	119 (2.5)	211 (2.3)
2- 3 Years	121 (2.6)	137 (2.9)	258 (2.8)
3- 4 Years	2669 (57.2)	2637 (56.4)	5306 (56.8)
4- 5 Years	1709 (36.6)	1696 (36.3)	3405 (36.5)
5- 6 Years	10 (0.2)	15 (0.3)	25 (0.3)

N: Number of participants, %: Percentage of participants,
Observation time defined as duration in study including periods off-treatment with investigational product.

Table 2-19 Proportion of exposure according to liraglutide dose – LEADER trial

Dose (mg.)	Lira (%)
0.6	5.5
1.2	9.6
1.8	84.8

Exposure divided into the per-protocol doses of liraglutide including the in-total two-weeks dose escalation period from 0.6 mg. to 1.2 mg. and 1.2 mg. to 1.8 mg. respectively after randomisation.

Table 2-20 Observation time by age group, gender and by treatment – LEADER trial

T2D Participants Age range	Lira N (observation time, PYO)			Placebo N (observation time, PYO)		
	Male	Female	Total	Male	Female	Total
Adults (18-64 years)	1602 (6196)	910 (3510)	2512 (9706)	1615 (6156)	884 (3385)	2499 (9541)
Elderly (65-74 years)	1141 (4297)	597 (2262)	1738 (6559)	1113 (4263)	642 (2421)	1755 (6684)
Elderly (75-84 years)	256 (968)	145 (532)	401 (1500)	251 (915)	142 (531)	393 (1446)

Elderly (85+ years)	12 (42)	5 (16)	17 (57)	13 (38)	12 (33)	25 (71)
Total	3011 (11503)	1657 (6320)	4668 (17822)	2992 (11371)	1680 (6370)	4672 (17741)

PYO: Patient years of observation time

Glycaemic control studies

Figure 2-2, Table 2-21, Table 2-22 and Table 2-23 show exposure to liraglutide in the completed therapeutic exploratory/confirmatory glycaemic control studies conducted with liraglutide in the T2D clinical development programme.

Participants were exposed to liraglutide for >42 months. A slightly higher percentage of males (57%) were exposed to liraglutide as compared to females (43%) in these studies. The majority of the participants exposed to liraglutide were adults aged between 18 and 64 years (77%), and of White (56%) or Asian (16%) origin. A similar pattern was observed for the other two treatment groups.

Figure 2-2 Number of participants by duration of exposure to liraglutide and comparators in completed exploratory and confirmatory studies – Liraglutide in T2D

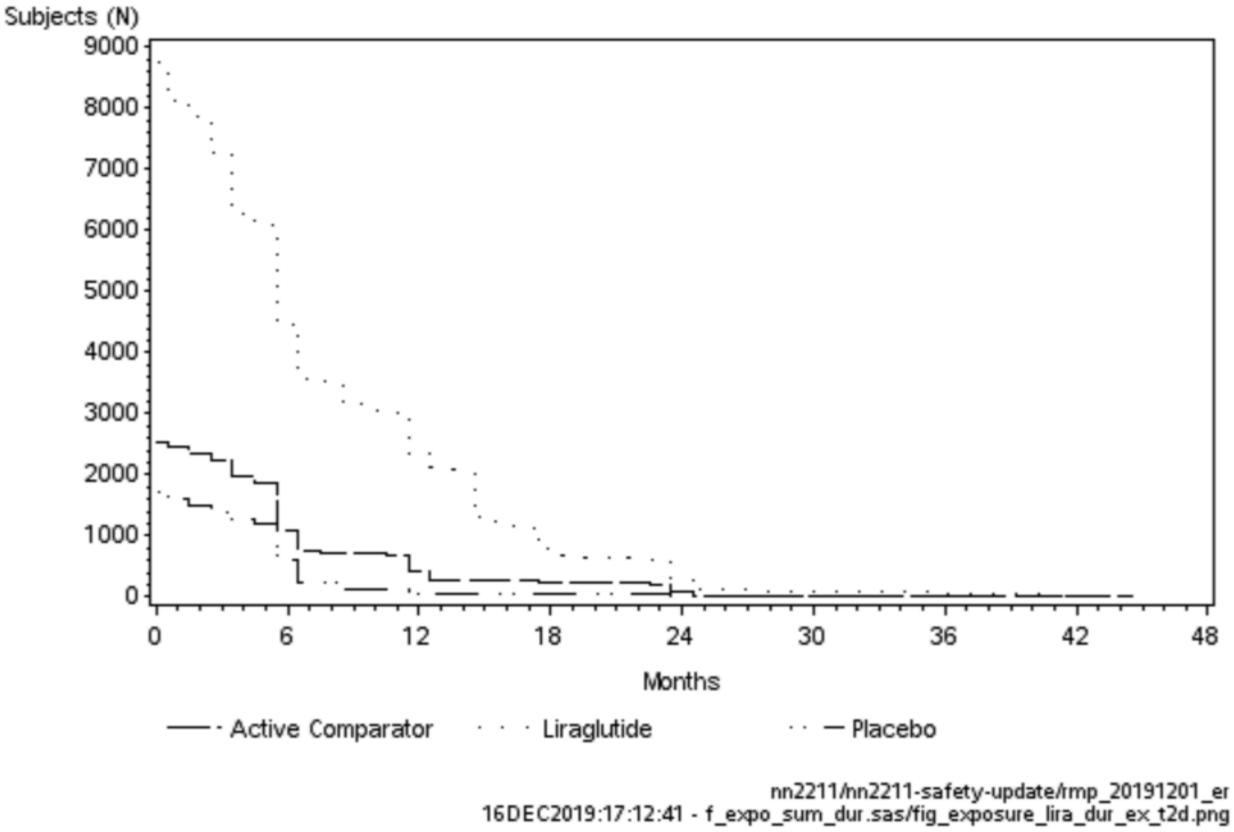


Table 2-21 Cumulative exposure to liraglutide in completed exploratory and confirmatory studies by dose – Liraglutide in T2D

Population	Dose group	Treatment	Number of participants	PYE
T2D	< 0.6 mg	Liraglutide	351	63.3
	0.6 mg	Liraglutide	927	630.8
	0.7-0.8 mg	Liraglutide	109	24.7
	0.9 mg	Liraglutide	1168	842.7
	1.0-1.1 mg	Liraglutide	68	1.5
	1.2 mg	Liraglutide	1417	1226.5
	1.3-1.7 mg	Liraglutide	103	11.7
	1.8 mg	Liraglutide	4698	3652.8
	1.9-2.3 mg	Liraglutide	101	12.6
	Total	Liraglutide	8750	6466.7

PYE: Participant years of exposure.
Cumulative reporting period ending 31 Oct 2019.
Confirmatory studies included: NN2211-1310, 1332, 1333, 1334, 1436, 1499, 1571, 1572, 1573(including extension 3529 trial), 1574, 1697, 1700, 1701, 1796, 1797, 1799, 1842, 1860, 2072, 3659, 3867, 3916, 3917, 3924, 3925, 3987, 4059, 4075, 4174, 4315.

Table 2-22 Cumulative exposure to liraglutide and comparators in completed exploratory and confirmatory studies by population, age range and gender – Liraglutide in T2D

		Liraglutide			Active Comparator			Placebo			Comparator pooled		
Population	Age range	Male N (PYE)	Female N (PYE)	Total N (PYE)	Male N (PYE)	Female N (PYE)	Total N (PYE)	Male N (PYE)	Female N (PYE)	Total N (PYE)	Male N (PYE)	Female N (PYE)	Total N (PYE)
T2D	Children	2	5	7	0	0	0	3	6	9	3	6	9
	2-11 yrs	(2.0)	(2.9)	(4.9)	(0.0)	(0.0)	(0.0)	(1.1)	(2.4)	(3.5)	(1.1)	(2.4)	(3.5)
	Adolescents	23	36	59	0	0	0	23	36	59	23	36	59
	12-17 yrs	(22.0)	(32.7)	(54.7)	(0.0)	(0.0)	(0.0)	(10.6)	(17.2)	(27.8)	(10.6)	(17.2)	(27.8)
	Adults	3849	2936	6785	1140	886	2026	716	492	1208	1856	1378	3234
	18-64 yrs	(2845.3)	(2216.2)	(5061.5)	(791.5)	(588.9)	(1380.4)	(346.7)	(231.9)	(578.6)	(1138.2)	(820.8)	(1959.1)
	Elderly	981	683	1664	247	184	431	188	185	373	435	369	804
	65-74 yrs	(692.2)	(492.4)	(1184.6)	(178.9)	(120.7)	(299.6)	(93.9)	(91.2)	(185.1)	(272.7)	(211.9)	(484.7)
	Elderly 75+	138	97	235	41	24	65	29	24	53	70	48	118
	yrs	(98.7)	(62.3)	(161.0)	(23.1)	(17.6)	(40.7)	(13.2)	(12.3)	(25.5)	(36.3)	(29.9)	(66.2)
	Total	4993	3757	8750	1428	1094	2522	959	743	1702	2387	1837	4224
		(3660.3)	(2806.4)	(6466.7)	(993.5)	(727.3)	(1720.7)	(465.5)	(355.1)	(820.6)	(1459.0)	(1082.4)	(2541.3)

N: Number of participant, PYE: Participant years of exposure.
Cumulative reporting period ending 31 Oct 2019.
Confirmatory studies included: NN2211-1310, 1332, 1333, 1334, 1436, 1499, 1571, 1572, 1573(including extension 3529 trial),1574, 1697, 1700, 1701, 1796, 1797, 1799, 1842,1860, 2072, 3659, 3867, 3916, 3917, 3924, 3925, 3987, 4059, 4075, 4174, 4315.
Active comparators: Oral anti diabetics, Exenatide, Glargine, Glibenclamide, Glimepiride,Insulin Degludec, Lixisenatide, Sitagliptine, Sulfonylurea.

Table 2-23 Cumulative exposure to liraglutide and comparators in completed exploratory and confirmatory studies by racial group − Liraglutide in T2D

Population	Racial group	Liraglutide N	Liraglutide PYE	Active Comparator N	Active Comparator PYE	Placebo N	Placebo PYE	Comparator pooled N	Comparator pooled PYE
T2D	AMERICAN INDIAN OR ALASKA NATIVE	9	5.3	1	0.3	5	1.8	6	2.1
	ASIAN	1439	680.4	632	313.4	214	126.7	846	440.1
	ASIAN INDIAN	1	0.1	0	0	0	0	0	0
	ASIAN NON-INDIAN	2	0.8	0	0	1	0.5	1	0.5
	ASIAN/NATIVE HAWAIIAN/PACIFIC ISLANDER	346	224.1	139	79.4	64	34.7	203	114.1
	BLACK OR AFRICAN AMERICAN	326	277.5	70	59.1	54	22.6	124	81.8
	HISPANIC OR LATINO	74	42.7	0	0	58	27.8	58	27.8
	JAPANESE	1258	916.7	132	119.7	134	85.0	266	204.7
	NA	20	8.8	10	4.4	0	0	10	4.4
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	6	4.0	1	1.0	1	0.0	2	1.1
	NOT HISPANIC OR LATINO	194	112.7	0	0	110	51.1	110	51.1
	UNKNOWN	11	5.0	12	5.9	5	2.1	17	8.0
	WHITE	4937	4067.0	1467	1089.9	1043	462.9	2510	1552.7
	OTHER	127	121.5	58	47.6	13	5.3	71	53.0

PYE: Participant years of exposure.
Cumulative reporting period ending 31 Oct 2019.
Confirmatory studies included: NN2211-1310, 1332, 1333, 1334, 1436, 1499, 1571, 1572, 1573(including extension 3529 trial), 1574, 1697, 1700, 1701, 1796, 1797, 1799, 1842, 1860, 2072, 3659, 3867, 3916, 3917, 3924, 3925, 3987, 4059, 4075, 4174,4315.
Active comparators: Oral anti diabetics, Exenatide, Glargine, Glibenclamide, Glimepiride, Insulin Degludec, Lixisenatide, Sitagliptine, Sulfonylurea.

2.3.3.2 Liraglutide in WM

Figure 2-3, Table 2-24, Table 2-25 and Table 2-26 show exposure to liraglutide in the completed therapeutic exploratory/confirmatory studies conducted in participants with overweight or obesity.

Participants were exposed to liraglutide for >37 months in the clinical development programme. The majority of the participants exposed to liraglutide were females (~71%), and adults aged between 18 and 64 years (88%). The majority of the participants were of White origin (85.5%). A similar pattern was observed for the placebo and active comparator groups.

Figure 2-3 Number of participants by duration of exposure to liraglutide and comparators in completed exploratory and confirmatory studies − Liraglutide in WM

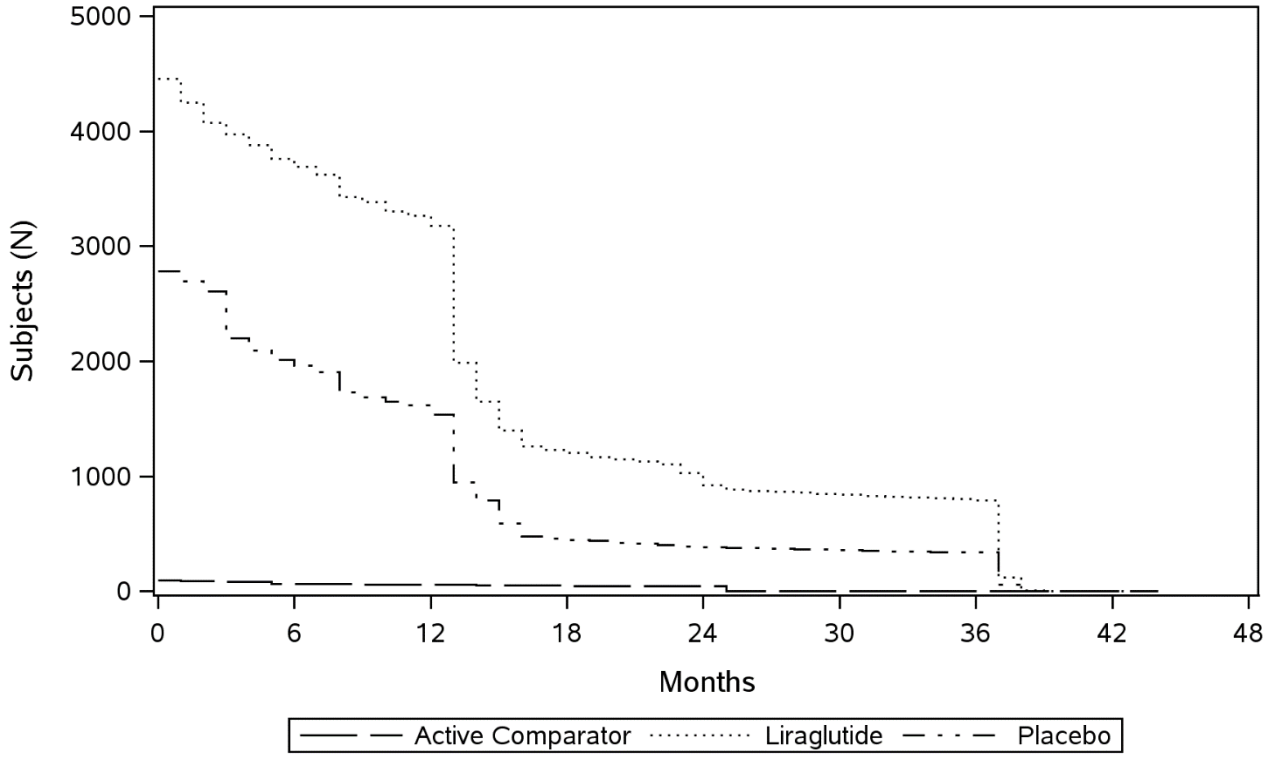


Table 2-24 Cumulative exposure to liraglutide in completed exploratory and confirmatory studies by dose − Liraglutide in WM

studies

Population	Dose group	Treatment	Number of participants	PYE
Exploratory/confirmatory clinical studies				
WM	1.2 mg	Liraglutide	95	72.9
	1.8 mg	Liraglutide	300	255.8
	2.4 mg	Liraglutide	335	254.4
	3.0 mg	Liraglutide	4098	5450.3
	Total	Liraglutide	4452	6033.5

PYE: Participants years of exposure.
Cumulative reporting period ending 31 Mar 2024.
Confirmatory studies included: NN8022-1807, 1839, 1922, 1923, 3970, 4272, 4274, 4180, 4392.
WM: Weight Management.

Table 2-25 Cumulative exposure to liraglutide and comparators in completed exploratory and confirmatory studies by population, age range and gender − Liraglutide in WM

		Liraglutide			Active Comparator			Placebo			Comparator pooled		
Population	Age range	Male N (PYE)	Female N (PYE)	Total N (PYE)	Male N (PYE)	Female N (PYE)	Total N (PYE)	Male N (PYE)	Female N (PYE)	Total N (PYE)	Male N (PYE)	Female N (PYE)	Total N (PYE)
WM	Children	26	25	51	0	0	0	13	11	24	13	11	24
	2-11 years	(25.5)	(22.8)	(48.3)	(0.0)	(0.0)	(0.0)	(13.8)	(9.8)	(23.7)	(13.8)	(9.8)	(23.7)
	Adolescents	58	72	130	0	0	0	49	79	128	49	79	128
	12-17 years	(57.9)	(67.3)	(125.2)	(0.0)	(0.0)	(0.0)	(47.4)	(74.9)	(122.3)	(47.4)	(74.9)	(122.3)
	Adults	1084	2867	3951	22	73	95	683	1756	2439	705	1829	2534
	18-64 years	(1427.5)	(4007.6)	(5435.1)	(26.5)	(95.2)	(121.8)	(703.7)	(1911.7)	(2615.4)	(730.3)	(2006.9)	(2737.2)
	Elderly	139	155	294	0	0	0	64	114	178	64	114	178
	65-74 years	(168.0)	(232.3)	(400.3)	(0.0)	(0.0)	(0.0)	(88.6)	(142.6)	(231.2)	(88.6)	(142.6)	(231.2)
	Elderly 75+ years	14 (9.0)	12 (15.6)	26 (24.6)	0 (0.0)	0 (0.0)	0 (0.0)	7 (7.2)	5 (7.0)	12 (14.2)	7 (7.2)	5 (7.0)	12 (14.2)
	Total	1321 (1688.0)	3131 (4345.6)	4452 (6033.5)	22 (26.5)	73 (95.2)	95 (121.8)	816 (860.7)	1965 (2146.0)	2781 (3006.7)	838 (887.2)	2038 (2241.3)	2876 (3128.5)

N: Number of participant, PYE: Participant years of exposure.
Cumulative reporting period ending 31 Mar 2024.
Confirmatory studies included: NN8022-1807, 1839, 1922, 1923, 3970, 4272, 4274, 4180, 4392.
Active comparators: Orlistat.
In cases were participants changed treatment arms, the percentage of participants does not add to 100.
WM: Weight management.

studies

Table 2-26 Cumulative exposure to liraglutide and comparators in completed exploratory and confirmatory studies by racial group − Liraglutide in WM

Population	Racial group	Liraglutide N	Liraglutide PYE	Active Comparator N	Active Comparator PYE	Placebo N	Placebo PYE	Comparator pooled N	Comparator pooled PYE
Exploratory/confirmatory clinical studies									
WM	AMERICAN INDIAN OR ALASKA NATIVE	12	11.5	1	2.0	5	8.1	6	10.1
	ASIAN	132	216.6	0	0	67	102.9	67	102.9
	BLACK OR AFRICAN AMERICAN	440	544.5	1	0.9	283	263.8	284	264.7
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	8	9.5	0	0	4	4.5	4	4.5
	NOT APPLICABLE	2	2.1	0	0	1	0.3	1	0.3
	WHITE	3781	5155.6	93	118.8	2382	2604.7	2475	2723.5
	OTHER	77	93.8	0	0	39	22.5	39	22.5

PYE: Participant years of exposure.
Cumulative reporting period ending 31 Mar 2024.
Confirmatory studies included: NN8022-1807, 1839, 1922, 1923, 3970, 4272, 4274, 4180, 4392.
Active comparators: Orlistat.
WM: Weight Management.

studies

2.4 Module SIV: Populations not studied in clinical studies

2.4.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 2-27 Exclusion criteria in pivotal clinical studies within the development programme – Liraglutide in T2D

Criteria	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Known or suspected hypersensitivity to the active substances or an excipient	If a participant with known or suspected hypersensitivity is exposed to one of these, a life-threatening condition could occur.	No Contraindications (SmPC Section 4.3) included: Hypersensitivity to liraglutide or to any of the excipients listed in Section 6.1.
Female of child-bearing potential, who is pregnant, breast-feeding or is not using adequate contraceptive methods	These participants were excluded as they are not intended to use 'liraglutide in T2D' and in order not to jeopardise their safety.	No Section 4.6 of the SmPC states that liraglutide should not be used during pregnancy and breast-feeding.
Children below 10 years of age	The efficacy and safety of 'liraglutide in T2D'is investigated within the agreed paediatric investigation plan (PIP). These participants were excluded from other studies as they are not currently intended to use the product.	No Victoza® is indicated for use in adults, adolescents and children aged 10 years and above.
Screening calcitonin value ≥ 50 ng/L and Personal or family history of medullary thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2).	Calcitonin levels >100 ng/L are highly predictive of MTC,[97] while the interpretation of values between the UNL and 100 ng/L is more uncertain. The limit was chosen in order not to include participants with a pre-existing risk of MTC. Patients with personal or family history of MTC or MEN2 are at an inherent high risk of MTC.	No MTC is considered an important potential risk for liraglutide in T2D (see Section 2.7.3).
Diagnosis of malignant neoplasm in the previous 5 years (except basal cell skin cancer or squamous cell skin cancer)	These participants were excluded in order to ensure the exclusion of serious diseases that could potentially interfere with study schedule, study procedures and study results. Basal cell skin cancer and squamous cell skin cancer were allowed as they are not associated with a high mortality risk.	No 'Neoplasms (including malignant melanoma)' is considered an important potential risk (see Section 2.7.3).

Criteria	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Participants with severe hepatic impairment	These participants are excluded in order to ensure the exclusion of serious diseases that could potentially interfere with study schedule, study procedures and study results, and in order not to jeopardise participants' safety.	No Patients with mild and moderate hepatic impairment were exposed to liraglutide in clinical studies (see Table 2-30). Safety profile of liraglutide was not identified to be different in patients with mild to moderate hepatic impairment. Recommendation against use in patients with severe hepatic impairment is included in the SmPC and PL to ensure safety in this population.
Participants with end-stage renal disease	These participants are excluded in order to ensure the exclusion of serious diseases that could potentially interfere with study schedule, study procedures and study results, and in order not to jeopardise participants' safety.	No Recommendation against use in patients with end-stage renal disease is included in the SmPC and PL to ensure safety in this population.
Heart failure, New York Heart Association (NYHA) class IV	These participants cannot carry out any physical activity. They are excluded in order to ensure the exclusion of serious diseases that could potentially interfere with study schedule, study procedures and study results, and in order not to jeopardise participants' safety.	No Recommendation against use in patients with heart failure NYHA IV is included in the SmPC and PL to ensure safety in this population.

Abbreviations: ALAT = alanine aminotransferase; MEN2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid cancer; PIP = paediatric investigation plan; PL = package leaflet; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes mellitus; UNL = upper normal limit.

Table 2-28 Exclusion criteria in pivotal clinical studies within the development programme – Liraglutide in WM

Criteria	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Known or suspected hypersensitivity to the active substances or an excipient	Events of known or suspected hypersensitivity to the active substances or the excipients in 'liraglutide in WM' are very rare. If a participant with known or suspected hypersensitivity is exposed to one of these, a life-threatening condition could occur.	No Contraindications (SmPC Section 4.3) included: Hypersensitivity to liraglutide or to any of the excipients listed in Section 6.1.
Female of child-bearing potential, who is pregnant, breast-feeding or is not using adequate contraceptive methods	These participants were excluded as they are not intended to use 'liraglutide in WM' and in order not to jeopardise their safety.	No Section 4.6 of the SmPC explicitly states that liraglutide should not be used during pregnancy and breast-feeding.
Children below 6 years of agebody weight ≤45 kg	These participants were excluded as they are not currently intended to use 'liraglutide in WM'. The efficacy and safety of the product is investigated within the agreed paediatric investigation plan (PIP).	No Saxenda® is indicated for use in adult and paediatric patients aged 6 years and above with body weight >45 kg.
Screening calcitonin value ≥50 ng/L and Personal or family history of medullary thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2).	Calcitonin levels >100 ng/L are highly predictive of MTC,[97] while the interpretation of values between the UNL and 100 ng/L is more uncertain. The limit was chosen in order not to include participants with a pre-existing risk of MTC. MTC is a potential risk from liraglutide nonclinical development. The participants with personal or family history of MTC or MEN2 are at an inherent high risk of MTC and are therefore excluded.	No MTC is considered an important potential risk for liraglutide in WM (see Section 2.7.3)
Untreated or uncontrolled hypothyroidism/hyperthyroidism defined as TSH >6 mIU/L or <0.4 mIU/L	These participants are excluded in order to ensure the exclusion of serious diseases that could potentially interfere with study schedule, study procedure or study results	No The safety profile is not expected to be different in this population.
Cancer, when judged by investigator that it could interfere with the results of the trial.	These participants are excluded in order to ensure the exclusion of serious diseases that could potentially interfere with study schedule, study procedure or study results	No 'Neoplasms (including malignant melanoma)' is considered an important potential risk (see Section 2.7.3)
Obesity induced by other endocrinological disorders (e.g., Cushing syndrome)	These participants were excluded in order to ensure the exclusion of serious diseases that could potentially interfere with study schedule, study procedure or study results.	No The safety profile is not expected to be different in this population.

Criteria	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Previous surgical treatment for obesity	Previous surgical treatment for obesity could potentially confound study results.	No The safety profile is not expected to be different in this population.
History of major depressive disorder within the last 2 years	These participants were excluded in order to ensure the exclusion of serious diseases that could potentially interfere with study schedule, study procedure or study results.	Yes
History of other severe psychiatric disorders (e.g., schizophrenia, bipolar disorder) or suicidal behaviour	These participants were excluded in order to ensure the exclusion of serious diseases that could potentially interfere with study schedule, study procedure or study results.	Yes

Abbreviations: MEN2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid cancer; PIP = paediatric investigation plan; SmPC = Summary of Product Characteristics; UNL = upper normal limit; TSH = thyroid-stimulating hormone.

2.4.2 Limitations of ADR detection common to clinical study development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.3 Limitations with respect to populations typically under-represented in clinical study development programmes

Table 2-29, Table 2-30 and Table 2-31 provide an overview of exposure in special populations in LEADER study, other glycaemic control studies and weight management studies, respectively. The development programme for WM is based on the same clinical pharmacological studies as the development programme for T2D.

Table 2-29 Exposure to liraglutide in special populations – LEADER trial

	Lira N	Placebo N
NYHA Class		
No heart failure		
FAS	**3836**	**3851**
PYO	**14775**	**14745**
NYHA class I		
FAS	179	169
PYO	672	626
NYHA class II		
FAS	545	546
PYO	1982	1984
NYHA class III		
FAS	108	106
PYO	393	387
Renal function (eGFR-MDRD)		
Normal renal function (eGFR-MDRD >=90 ml/min/1.73m^2)		

FAS	1620	1655
PYO	6269	6346
Mild renal impairment (eGFR-MDRD >=60 and <90 ml/min/1.73m²)		
FAS	1932	1975
PYO	7408	7582
Moderate renal impairment (eGFR-MDRD >=30 and <60 ml/min/1.73m²)		
FAS	999	935
PYO	3740	3446
Severe renal impairment (eGFR-MDRD <30 ml/min/1.73m²)		
FAS	117	107
PYO	405	366

Lira: Liraglutide, FAS: Full analysis set, N: Number of participants, eGFR-MDRD: Estimated glomerular filtration rate using the modification of diet in renal disease formula, MACE: Major cardiovascular event, EAC: event adjudication committee, MDRD: modification of diet in renal disease, NYHA: New York Heart Association, PYO: Patient years of observation, Heart failure and unstable angina pectoris requiring hospitalisation.

Table 2-30 Exposure to liraglutide in special populations – adult participants – T2D programme

Population/ Indication	Special population	Liraglutide N	PYE
Clinical pharmacology clinical studies	Pregnant women	N/A	
	Lactating women	N/A	
	Renal impairment		
	Mild	6	0.0
	Moderate	7	0.0
	Severe	16	0.0
	Hepatic impairment	24	0.1
	Cardiac impairment	N/A	
	Sub-populations with genetic polymorphism	N/A	
	Immunocompromised	N/A	
Exploratory/confirmatory glycaemic control studies	Pregnant women	N/A	
	Lactating women	N/A	
	Renal impairment		
	Mild	N/A	
	Moderate	140	57.5
	Severe	N/A	
	Hepatic impairment	N/A	
	Cardiac impairment	N/A	
Exploratory/confirmatory clinical studies	Sub-populations with genetic polymorphism	N/A	
	Immunocompromised	N/A	

T2D: Type 2 Diabetes mellitus
N: Number of participants, PYE: Participant years of exposure, eGFR: estimated glomerular filtration rate
Pharmacology studies included: NN2211-1328, 1329
Confirmatory studies included: NN2211-3916
Renal impairment is according to CKD-EPI formula as follows:
Mild renal impairment (based on eGFR) 60-89 mL/min per 1.73 m^2
Moderate renal impairment (based on eGFR) 30-59 mL/min per 1.73 m^2
Severe renal impairment (based on eGFR) <30 mL/min per 1.73 m^2
For study NN2211-1329, participants with normal renal function were excluded from this table.
N/A: Not applicable - no study finalised in the specific population

Table 2-31 Exposure to liraglutide in special populations – adult participants – Weight management programme

Population/ Indication	Special population	Liraglutide N	PYE
Clinical pharmacology clinical studies	Pregnant women	N/A	
	Lactating women	N/A	
	Renal impairment		
	Mild	N/A	
	Moderate	N/A	
	Severe	N/A	
	Hepatic impairment	N/A	
	Cardiac impairment	N/A	
	Sub-populations with genetic polymorphism	N/A	
	Immunocompromised	N/A	
Exploratory/confirmatory clinical studies	Pregnant women	N/A	
	Lactating women	N/A	
	Renal impairment		
	Mild	1698	2503.2
	Moderate	181	273.3
	Severe	4	7.3
	Hepatic impairment	N/A	
	Cardiac impairment	N/A	
	Sub-populations with genetic polymorphism	N/A	
	Immunocompromised	N/A	

WM: Weight management
N: Number of participants, PYE: Participant years of exposure, eGFR: estimated glomerular filtration rate
Pharmacology studies included: NN8022-3630, 3967, 4162
Confirmatory studies included: NN8022-1807, 1839, 1922, 1923, 3970
Mild renal impairment (based on eGFR) 60-89 mL/min per 1.73 m^2
Moderate renal impairment (based on eGFR) 30-59 mL/min per 1.73 m^2
Severe renal impairment (based on eGFR) <30 mL/min per 1.73 m^2
N/A: Not applicable - no study finalised in the specific population

The target population for marketed use of 'liraglutide in T2D' and 'liraglutide in WM' is comparable to the patient population included in the clinical development programme. No safety concerns were identified or anticipated in any of the sub-populations which classify them as missing information.

2.5 Module SV: Post-authorisation experience

2.5.1 Post-authorisation exposure

2.5.1.1 Method used to calculate exposure

The sales figures are based on the total volume (including samples) of liraglutide in T2D and WM released from Novo Nordisk to external customers cumulatively.

Exposure data for 'liraglutide in T2D' have been calculated from the released total volume of the product, assuming an average daily dose of 1.2 mg and the exposure data for 'liraglutide in WM' have been calculated from the released total amount of the product, assuming an average daily dose of 3.0 mg. As the estimated exposure is based on volume distributed to external customers and average daily usage rather than actual patient exposure, the numbers may be over- or underestimated.

It is not possible to estimate liraglutide post-marketing exposure by age group, gender or indication, since these estimates are based on total sales volume, and not on prescription data.

2.5.1.2 Exposure

Liraglutide in T2D

The first marketing authorisation for 'liraglutide in T2D' was received in the EU on 30 Jun 2009, and the product was first launched in Denmark (03 Jul 2009). Estimates of accumulated exposure to 'liraglutide in T2D' from post-authorisation experience since marketing authorisation are shown in Table 2-32.

Table 2-32 Estimated exposure to 'liraglutide in T2D' by region from post-authorisation experience

Region	Exposure (PYE)
EU[a]	4,576,053
Non-EU	11,471,696
Total	**16,047,749**

Note: Exposure data for 'liraglutide in T2D' have been calculated based on the total volume of Victoza® (expressed in grams (G)) distributed to external customers.

PYE = (G ×1,000)/(1.2×365); average daily dose (as defined by the WHO) = 1.2 mg.

[a]EU includes all EEA countries.

Abbreviations: EEA = European Economic Area; PYE = patient-years of exposure; T2D = type 2 diabetes mellitus.

Liraglutide in WM

The first marketing authorisation for 'liraglutide in WM' was received in the US on 23 Dec 2014 and the product was first launched in the US (20 Apr 2015). The product received marketing authorisation in the EU on 23 Mar 2015 and was launched on 17 Aug 2015 in Denmark. Estimates of accumulated exposure to 'liraglutide in WM' from post-authorisation experience since marketing authorisation are shown in Table 2-33.

Table 2-33 Estimated exposure to 'liraglutide in WM' by region from post-authorisation experience

Region	Exposure (PYE)
EU[a]	437,088
Non-EU	1,577,023
Total	**2,014,111**

Note: Exposure data for 'liraglutide in WM' have been calculated based on the total volume of Saxenda® (expressed in grams (G)) distributed to external customers.

PYE = (G ×1,000)/(3.0×365); average daily dose = 3.0 mg.

Cumulative period ending 31 Mar 2024.

[a]EU includes all EEA countries including Switzerland and United Kingdom.

Abbreviations: EEA = European Economic Area; PYE = patient-years of exposure; WM = weight management.

2.5.2 Post-authorisation use and off-label use

The post-marketing spontaneous reports show generally low off-label use of liraglutide. Due to poor data quality in spontaneous reports, a high proportion of cases do not have the indication reported, which is why a detailed presentation of cases with off-label use by indication is not meaningful. However, the cases related to off-label use received do not raise any safety concerns as the indications reported and the co-reported events are in line with the known safety profile of 'liraglutide in T2D' and 'liraglutide in WM'. Overall, the ADR profile from off-label use cases is not different from the ADR profile for the indicated uses of liraglutide.

Novo Nordisk conducted two drug utilisation studies (DUS) categorized as post-authorization safety studies (PASS), NN8022-4241 and NN8022-4246 as required by the EMA. The scope of these PASS was primarily to assess the use of Saxenda® according to the approved indication, and also the use of Victoza® for the treatment of weight management in routine clinical practice. The studies involved retrospective review of medical records in two selected EU countries (Italy and Germany, study NN8022-4241) and the Clinical Practice Research Datalink (CPRD) primary care and diagnostic data, combined with additional information obtained from general practitioner questionnaire, in the United Kingdom (study NN8022-4246). Despite the extent of missing data encountered, the real-world data from these studies supported the prescribers' general adherence to the approved indications for Saxenda® and Victoza®, with an observed minor degree of non-adherence to their labelling. The results from these PASS did not give rise to any new safety concerns for liraglutide.

Study NN8022-4241

The results from the PASS NN8022-4241 showed that Saxenda® was mainly prescribed to patients with obesity (70 patients out of 75; 93.3%). No patients were prescribed any other GLP-1 receptor agonist during the treatment with Saxenda®. Furthermore, the results showed that 99.3% of patients were prescribed Victoza® for T2D (out of 150 patients, 1 patient received Victoza® for weight management and 1 patient was reported as receiving 3.0 mg dose of Victoza®).

Study NN8022-4246

The PASS conducted in the UK (NN8022-4246) describes the real-world usage of liraglutide based on data from 604 patients who were prescribed Saxenda®, 4,868 patients prescribed Victoza®, and 7,895 patients prescribed unbranded liraglutide in the UK. The study report provides descriptive data for initiators of liraglutide in the initial 5 years period post-launch of Saxenda® in the UK.

This study suggests that Saxenda® is mostly prescribed according to its approved indication with a minor degree of non-adherence to the labelling (11 patients of the 306 with a valid BMI at treatment initiation date; 3.6%). Nearly half (49%) of the patients who were prescribed Saxenda® did not have a valid BMI recorded at treatment initiation date. Adherence to the stopping rule and dose escalation were difficult to interpret due to missing relevant information in the databases.

The use of Victoza® also seemed to be mostly according to the approved dose, with an observed non-adherence to its labelling of 2.2% (2 patients out of 92 with recorded dose at treatment initiation date). The non-adherence was related to a daily dose of 3.0 mg which corresponds to the dose used for weight management. A total of 2,115 (44%) patients on Victoza® had at least one occurrence of a short prescription interval, potentially corresponding to a daily dose of 3.0 mg,

however, this observation probably reflects real world prescription patterns where physicians prescribe according to practical needs of the patients (e.g., vacation). Similar results to Victoza® were observed for the prescriptions of unbranded liraglutide.

2.6 Module SVI: Additional EU requirements for the safety specification

2.6.1 Potential for misuse for illegal purposes – Liraglutide in T2D and weight management

Currently, no potential for misuse has been identified. The potential for use as a recreational drug or as a drug facilitating assault is very limited. Liraglutide is not considered to belong to the classical drug abuse categories of opiates and narcotics, central nervous system stimulants/depressants, hallucinogens or cannabinoids based on extensive receptor binding studies, as well as the nonclinical studies of cardiovascular effects, body temperature and locomotor activity. Overdosing will, in a worst-case scenario, result in severe gastrointestinal adverse events. Furthermore, liraglutide is not known to be addictive.

2.7 Module SVII: Identified and potential risks

2.7.1 Identification of safety concerns in the initial RMP submission

This section is not applicable as the initial RMP for liraglutide was submitted prior to the implementation of GVP Module V – Risk management systems (Rev 2).

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns including important potential or identified risks for liraglutide in T2D and WM have been identified.

The missing information ‘off-label use’ was removed from the list of RMP safety concerns following the Committee for Medicinal Products for Human Use (CHMP)/Pharmacovigilance Risk Assessment Committee (PRAC) assessment report for the liraglutide RMP version 33.0 (EMEA/H/C/003780/II/0034).

Novo Nordisk will continue to monitor off-label use for ‘liraglutide in T2D’ and ‘liraglutide in WM’ through routine pharmacovigilance activities and any new information concerning off-label use will be described regularly in the PSURs

2.7.3 Details of important identified risks, important potential risks, and missing information

2.7.3.1 General considerations

In the sections below, the clinical study data are presented separately for T2D and WM indications for each risk. In addition, the data from the CVOT LEADER and the paediatric studies (NN2211-3659 and NN8022-4180, -4392) are also presented separately where relevant. Further data from post-marketing sources (including spontaneous, solicited and literature reports) for ‘liraglutide in T2D’ and ‘liraglutide in WM’ are also included for each risk as relevant.

2.7.3.2 Important identified risks

There are no important identified risks included in the RMP for 'liraglutide inT2D' and 'liraglutide in WM'.

2.7.3.3 Important potential risk: Neoplasms (including melanoma)

'Neoplasms (including melanoma)' is an important potential risk for 'liraglutide inT2D' and 'liraglutide in WM'.

Potential mechanisms

Unknown

Evidence source and strength of evidence

In the T2D clinical development programme, an imbalance in neoplasm reporting rates (liraglutide > comparator) was seen at the time of marketing authorisation application (MAA). The rate of malignant neoplasms was comparable between participants treated with liraglutide and those not treated with liraglutide. Event adjudication was not applied, and the number of events was small.

In the CVOT EX2211-3748 (LEADER), similar proportions of participants in the liraglutide group and placebo group had EAC-confirmed neoplasms. A numerical imbalance in the low number of patients with *malignant melanoma of the skin* (liraglutide > comparator) was observed which resulted in a numerically higher rate of *malignant melanoma* observed for liraglutide (0.07 vs. 0.02 events per 100 PYO).

In the clinical development programme for 'liraglutide in WM', the reporting rates of overall neoplasm events confirmed by an event adjudication committee (EAC) were comparable for liraglutide and placebo at the time of MAA. However, a higher event rate of neoplasm-related SAEs was observed in the liraglutide arm compared to the placebo arm.

Based on the above considerations, neoplasm (including melanoma) has been classified as an important potential risk for liraglutide in T2D and WM.

Characterisation of the risk

Frequency, seriousness and outcome

Liraglutide in T2D

CVOT EX2211-3748 (LEADER): The proportions of participants with EAC-confirmed neoplasms overall was 10.1% and 9.0% in the liraglutide group and the placebo group respectively (3.6% vs. 3.1% for benign neoplasms and 6.3% vs. 6.0% for malignant neoplasms); for details see Table 2-34. No statistically significant treatment difference was shown. The majority of EAC-confirmed neoplasm events were malignant in both treatment groups with a hazard ratio (liraglutide vs. placebo) of 1.06 ($[0.90; 1.25]_{95\% CI}$) as estimated by a post hoc Cox regression analysis. No clustering within specific organ sites was observed for either treatment group.

Glycaemic control studies: The event rate of neoplasm-related events (both serious and non-serious) were low in the liraglutide group compared to placebo. The majority of the events were non-serious (~70%) and mild in severity (~65%) in both the treatment groups. Fatal outcome was reported for 4 events in the liraglutide group and none in the placebo group (Table 2-35).

Paediatric study (NN2211-3659): 3 neoplasm-related events were reported (2 in the liraglutide group and 1 in the placebo group), out of which 1 event was serious and was reported in the liraglutide treatment group. All events were assessed as unlikely related to the study product by the investigator. The outcome was reported as 'recovered' and 'recovering' for the 2 events in the liraglutide group, and 'not recovered' for the 1 event in the placebo group (Table 2-36).

Liraglutide in WM

Clinical study data

The overall event rate for neoplasm-related adverse events (serious and non-serious combined) was comparable between the two treatment arms. A higher event rate of neoplasm-related SAEs was observed in the liraglutide arm than in the placebo arm. The reason for this imbalance is unknown. A similar picture was observed with the neoplasm-related adverse events confirmed by an external event adjudication committee (EAC); see Table 2-37.

Paediatric study (NN8022-4180): 8 neoplasm-related events were reported (5 in the liraglutide group and 3 in the placebo group) all of which were benign in nature. None of the events in the liraglutide group were serious, severe in intensity or with a fatal outcome. One event in the liraglutide group was assessed as possibly/probably related to the study product by the investigator (Table 2-38).

Paediatric study (NN8022-4392): No neoplasm-related events were reported from this study (Table 2-39)

Table 2-34 Overview of EAC-confirmed overall neoplasm index events in the study EX2211-3748 (LEADER)

	Lira				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of participants	4668				4672			
Male	3011				2992			
Female	1657				1680			
PYO	17822				17741			
Male	11503				11371			
Female	6320				6370			
Number of events	470	(10.1)	595	3.34	419	(9.0)	528	2.98
Malignant	296	(6.3)	356	2.00	279	(6.0)	326	1.84
Pre-malignant	37	(0.8)	40	0.22	26	(0.6)	30	0.17
Benign	168	(3.6)	196	1.10	145	(3.1)	171	0.96
Unclassified	3	(0.1)	3	0.02	1	(0.0)	1	0.01

N: Number of participants, %: Proportion of participants, E: Number of events, R: Event rate per 100 observation years.
PYO: Patient years of observation, EAC: Event adjudication committee.
Index events with EAC onset date from randomisation date to follow-up are included. The index event is the event selected among multiple events if these were assessed and confirmed to be one and the same event.

Table 2-35 Overview of all treatment-emergent neoplasms in exploratory/confirmatory studies − Liraglutide in T2D

	Liraglutide [1],[2]				Placebo [2]				Active comparator			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
All participants	7331				1674				3020			
Exposure (years)	4862.7				799.8				2112.2			
All neoplasm events	194	(2.6)	229	47.1	32	(1.9)	40	50.0	69	(2.3)	80	37.9
Serious	54	(0.7)	55	11.3	10	(0.6)	11	13.8	19	(0.6)	19	9.0
Non-serious	147	(2.0)	174	35.8	25	(1.5)	29	36.3	53	(1.8)	61	28.9
Severe	30	(0.4)	30	6.2	3	(0.2)	4	5.0	9	(0.3)	9	4.3
Moderate	46	(0.6)	52	10.7	9	(0.5)	9	11.3	16	(0.5)	16	7.6
Mild	129	(1.8)	147	30.2	22	(1.3)	27	33.8	48	(1.6)	55	26.0
Unknown	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0
Missing	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0
Relation to study product												
Possibly/probably	18	(0.2)	21	4.3	3	(0.2)	3	3.8	3	(0.1)	3	1.4
Unlikely	173	(2.4)	203	41.7	28	(1.7)	36	45.0	48	(1.6)	54	25.6
Missing	5	(0.1)	5	1.0	1	(0.1)	1	1.3	19	(0.6)	23	10.9
Outcome												
Fatal	4	(0.1)	4	0.8	0	(0)	0	0	1	(0.0)	1	0.5
Recovered	92	(1.3)	104	21.4	15	(0.9)	16	20.0	31	(1.0)	35	16.6
Recovering	6	(0.1)	6	1.2	3	(0.2)	3	3.8	3	(0.1)	3	1.4
Recovered with sequelae	6	(0.1)	6	1.2	2	(0.1)	2	2.5	1	(0.0)	1	0.5
Not recovered	89	(1.2)	101	20.8	16	(1.0)	19	23.8	35	(1.2)	38	18.0
Remitted	5	(0.1)	5	1.0	0	(0)	0	0	2	(0.1)	2	0.9
Stabilised	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0
Unknown	3	(0.0)	3	0.6	0	(0)	0	0	0	(0)	0	0
Neoplasm events leading to withdrawals	23	(0.3)	23	4.7	0	(0)	0	0	7	(0.2)	7	3.3

N: Number of participants, %: Percentage of participants, E: Number of events,R: Rate (number of adverse events divided by patient years of exposure multiplied by 1000), MedDRA Version 22.1
[1] All liraglutide doses; [2] +/- Oral anti-diabetic add on
Relationship to study drug is based on investigator or EAC assessment.
Table only includes treatment emergent adverse events defined as adverse events occurring between first day on study product until last day on study product + 7 days (35 days for NN9535-1821).
Studies included: NN1250-3948, NN2211-1310, 1332, 1333, 1334, 1436, 1499, 1571, 1572, 1573, 1574, 1697, 1700, 1701, 1796, 1797-main, 1799, 1860-main, 1860-ext1, 2072, 3867, 3916, 3917, 3924, 3925, 3987, 4059, 4075, 4315, NN9535-1821, NN9068-3697-main-ext.
Active comparators: Oral anti diabetics, Exenatide, Glargine, Glibenclamide, Glimepiride, Insulin Degludec, Lixisenatide, Sitagliptine, Sulfonylurea.

Table 2-36 Overview of all treatment-emergent neoplasms in paediatric study with liraglutide in T2D − NN2211-3659

	Liraglutide [1],[2] N	(%)	E	R	Placebo [2] N	(%)	E	R
All participants	66				68			
Exposure (years)	59.6				59.2			
All neoplasm events	2	(3.0)	2	33.5	1	(1.5)	1	16.9
Serious	1	(1.5)	1	16.8	0	(0)	0	0
Non-serious	1	(1.5)	1	16.8	1	(1.5)	1	16.9
Severe	0	(0)	0	0	0	(0)	0	0
Moderate	1	(1.5)	1	16.8	1	(1.5)	1	16.9
Mild	1	(1.5)	1	16.8	0	(0)	0	0
Unknown	0	(0)	0	0	0	(0)	0	0
Missing	0	(0)	0	0	0	(0)	0	0
Relation to study product								
Possibly/probably	0	(0)	0	0	0	(0)	0	0
Unlikely	2	(3.0)	2	33.5	1	(1.5)	1	16.9
Missing	0	(0)	0	0	0	(0)	0	0
Outcome								
Fatal	0	(0)	0	0	0	(0)	0	0
Recovered	1	(1.5)	1	16.8	0	(0)	0	0
Recovering	1	(1.5)	1	16.8	0	(0)	0	0
Recovered with sequelae	0	(0)	0	0	0	(0)	0	0
Not recovered	0	(0)	0	0	1	(1.5)	1	16.9
Remitted	0	(0)	0	0	0	(0)	0	0
Stabilised	0	(0)	0	0	0	(0)	0	0
Unknown	0	(0)	0	0	0	(0)	0	0
Neoplasm events leading to withdrawals	0	(0)	0	0	0	(0)	0	0

N: Number of participants, %: Percentage of participants, E: Number of events, R: Event rate/1,000 exposure years, MedDRA Version 21.0
[1] All liraglutide doses
[2] +/- Oral anti-diabetic add on
Relationship to study drug is based on investigator
Table only includes treatment emergent adverse events defined as adverse events occurring between first day on study product until last day on study product + 7 days.
Active comparators: none

Liraglutide in WM

Table 2-37 Overview of EAC-confirmed all treatment-emergent neoplasm events in exploratory/confirmatory studies with liraglutide in WM

	Liraglutide [1],[2]				Placebo [2]			
	N	(%)	E	R	N	(%)	E	R
All participants	3501				1843			
Years of observation	5187.6				2453.0			
All EAC confirmed neoplasms events	98	(2.8)	106	20.4	45	(2.4)	53	21.6
Serious	44	(1.3)	46	8.9	11	(0.6)	12	4.9
Non-serious	57	(1.6)	58	11.2	35	(1.9)	41	16.7
Missing seriousness	2	(0.1)	2	0.4				
Severe	22	(0.6)	24	4.6	9	(0.5)	10	4.1
Moderate	27	(0.8)	27	5.2	11	(0.6)	12	4.9
Mild	50	(1.4)	53	10.2	29	(1.6)	31	12.6
Missing	2	(0.1)	2	0.4				
EAC confirmed neoplasms events leading to withdrawals	15	(0.4)	15	2.9	7	(0.4)	7	2.9

EAC: (external) Event adjudication committee; WM: Weight management
N: Number of participants, %: Percentage of participants, E: Number of events,
R: Event rate/1,000 exposure years, MedDRA Version 19.0
[1] All liraglutide doses
[2] +/- Oral anti-diabetic add on
Relationship to study drug is based on investigator(s)'s assessment or EAC.
Table only includes treatment emergent adverse events defined as adverse events occurring between first day on study product until last day on study product + 14 days.
Studies included: NN8022-1922, 1923, 3970 and 1839 (1-year and 3-year data)

Table 2-38 Overview of all treatment-emergent neoplasms in the paediatric study with liraglutide in WM – NN8022-4180

	Liraglutide [1],[2] N	(%)	E	R	Placebo [2] N	(%)	E	R
All participants	125				126			
Exposure (years)	125.6				124.9			
All neoplasm events	3	(2.4)	5	39.8	3	(2.4)	3	24.0
Serious	0	(0)	0	0	1	(0.8)	1	8.0
Non-serious	3	(2.4)	5	39.8	2	(1.6)	2	16.0
Severe	0	(0)	0	0	0	(0)	0	0
Moderate	1	(0.8)	1	8.0	3	(2.4)	3	24.0
Mild	3	(2.4)	4	31.9	0	(0)	0	0
Unknown	0	(0)	0	0	0	(0)	0	0
Missing	0	(0)	0	0	0	(0)	0	0
Relation to study product								
Possibly/probably	1	(0.8)	1	8.0	0	(0)	0	0
Unlikely	3	(2.4)	4	31.9	2	(1.6)	2	16.0
Missing	0	(0)	0	0	1	(0.8)	1	8.0
Outcome								
Fatal	0	(0)	0	0	0	(0)	0	0
Recovered	2	(1.6)	2	15.9	2	(1.6)	2	16.0
Recovering	1	(0.8)	2	15.9	0	(0)	0	0
Recovered with sequelae	0	(0)	0	0	0	(0)	0	0
Not recovered	1	(0.8)	1	8.0	1	(0.8)	1	8.0
Remitted	0	(0)	0	0	0	(0)	0	0
Stabilised	0	(0)	0	0	0	(0)	0	0

N: Number of participants, %: Percentage of participants, E: Number of events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 1000), MedDRA Version 22.1
[1] All liraglutide doses [2] +/- Oral anti-diabetic add on
Relationship to study drug is based on investigator assessment.
Table only includes treatment emergent adverse events defined as adverse events occurring between first day on study product until last day on study product + 14 days.
WM: Weight management.

Table 2-39 Overview of all treatment emergent neoplasms in the paediatric study with liraglutide in WM – NN8022 4392

There is no data for this table

Abbreviations: WM = weight management

Table 2-40 provides an overview of malignant melanoma events of skin from LEADER trial.

Table 2-40 Overview of EAC-confirmed malignant melanoma neoplasm index events of skin, Liraglutide in T2D − EX2211-3748 (LEADER)

	Lira				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of participants	4668				4672			
PYO	17822				17741			
EAC-confirmed melanoma of the skin								
Malignant	13	(0.3)	13	0.07	5	(0.1)	5	0.03

%: Proportion of events, E: Number of events, EAC: Event adjudication committee, FAS: Full analysis set, N: Number of participants, PYO: Patient years of observation, R: Event rate per 100 patient years of observation
Index events with EAC onset date from randomisation date to follow-up are included. The index event is the event selected among multiple events if these were assessed and confirmed to be one and the same event.

Background incidence and prevalence

Incidence of overall neoplasm

Incidence rate of overall neoplasm in participants with T2D is estimated to be 4.5 to 24.4 per 1,000 patient-years.[98-113]

Relative risk of overall neoplasm

Relative risk ratio of overall neoplasm in participants with T2D is estimated to be 1.1 to 1.8 for persons with diabetes compared with persons without diabetes.[69, 102-105, 109-111, 114-117]

Obesity is associated with increased risk of several cancer types. A working group was convened in 2016 by the International Agency for Research on Cancer (IARC) to review existing epidemiological evidence in order to assess this increased risk. They found sufficient evidence for the following cancer types and sites: oesophageal adenocarcinoma, gastric cardia, colon and rectum, liver, gallbladder, pancreas, postmenopausal breast cancer, corpus uteri, ovary, kidney (renal cell), meningioma, thyroid and multiple myeloma.[118]

Incidence of malignant melanoma

Incidence rate of malignant melanoma in participants with diabetes mellitus (not distinguished between T1D and T2D) is estimated to be 0.2 to 0.4 per 1,000 person-years in US studies (references do not specify organ localisations of the malignant melanomas).[119, 120] Incidence rate of non-melanoma skin cancer in participants with T2D is estimated to be 0.8 per 1,000 person-years.[121]

Pothiawala *et al*. studied the incidence of melanoma in two cohorts in the US, the Nurses' Health Study and the Health Professionals Follow-Up Study. No support for the hypothesis of increasing melanoma risk with higher levels of BMI was found.[122] The same conclusion was reached by a meta-analysis from 2013.[123]

No studies have been published specifying incidence rates of malignant melanoma by group of BMI.

Prevalence of overall neoplasms (including melanoma)

Unknown

Risk factors and risk groups

There is no indication of a causal relationship between liraglutide and the overall neoplasms. Patient risk factors for neoplasm include T2D, obesity, smoking, alcohol abuse, environmental factors, a history of neoplasm and genetic predisposition.

Preventability

No causal relationship has been established between liraglutide treatment and overall neoplasms; preventability is, therefore, not applicable.

Impact on the benefit-risk balance of the product

Neoplasms can have major impact on the patients' quality of life, and malignant neoplasms may result in death. Due to the potential impact on the patient's quality of life, 'Neoplasms (including melanoma)' is considered as an important potential risk for liraglutide in T2D and WM despite lack of established causal relationship.

However, based on the fact that a causal association could not be established, Novo Nordisk evaluates that the impact of consequences of 'Neoplasms (including melanoma)'on the benefit–risk profile of liraglutide is low.

Public health impact

Considering the extensive exposure to liraglutide in clinical studies and in post-marketing settings, the absolute risk is expected to be low and the potential impact on public health is expected to be minimal.

2.7.3.4 Important potential risk: Medullary thyroid cancer (C-cell carcinogenicity)

Medullary thyroid cancer (MTC; C-cell carcinogenicity) is an important potential risk for 'liraglutide inT2D' and 'liraglutide in WM'.

Potential mechanisms

Unknown

Evidence source and strength of evidence:

Thyroid C-cell tumours were observed in liraglutide carcinogenicity studies in mice and rats. Based on mechanistic data generated by Novo Nordisk and data from the literature, it has been shown that the C-cell tumours induced in mice and rats following dosing of liraglutide are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which mice and rats are particularly sensitive, whereas monkeys and humans are not. The relevance for humans is likely to be low.

Data based on the intensive monitoring of calcitonin (a marker for MTC) in plasma from the liraglutide clinical development programme do not support a liraglutide effect on calcitonin in humans.

Characterisation of the risk

Frequency, seriousness and outcome

Clinical study data

- Liraglutide in T2D – EX2211-3748 (LEADER): No cases of MTC were observed in liraglutide-treated participants. One event of medullary thyroid carcinoma was confirmed for a participant in the placebo group by the EAC.
- Liraglutide in T2D – Glycaemic control studies: A total of 2 events of MTC have been reported in the clinical studies of liraglutide in T2D. None of the events occurred in patients treated with liraglutide. No cases of MTC were observed in the paediatric study NN2211-3659.
- Liraglutide in WM: One serious treatment-emergent AE of MTC in the placebo group has been identified in the clinical studies, where the patient recovered from the event. No cases of MTC were observed in the paediatric studies NN8022-4180 (participants aged 12–18 years) and NN8022-4392 (participants aged 6–12 years; Table 2-41).

Table 2-41 Overview of all treatment emergent medullary thyroid cancer in the paediatric study with liraglutide in WM – NN8022 4392

There is no data for this table

Abbreviations: WM = weight management

Post-marketing data

- Liraglutide in T2D - A total of 54 events of MTC were received for 'liraglutide in T2D' from post-marketing sources (Table 2-42). Limited information regarding event onset details, diagnostic and laboratory test results, concomitant medications, other co-morbid conditions, lifestyle (smoking, alcohol use), family history of cancer and genetic syndromes, severity and outcome of the event was provided in the reported cases, hindering a thorough medical assessment.

Table 2-42 Overview of all MTC events from post-marketing sources, liraglutide in T2D

Product	Number of events (reporting rate [events per 1,000 PYE])	
	Serious	Non-serious
Liraglutide in T2D (Victoza®)	54 (0.003)	0 (0.000)

Abbreviations: MTC = medullary thyroid cancer; PYE = patient-years of exposure; T2D = type 2 diabetes mellitus; WM = weight management.

- Liraglutide in WM – A total of 4 events of MTC were received for with 'liraglutide in WM' from post-marketing sources Limited information regarding event onset details, diagnostic and

laboratory test results, concomitant medications, other co-morbid conditions, lifestyle (smoking, alcohol use), family history of cancer and genetic syndromes, severity and outcome of the event was provided in the reported cases, hindering a thorough medical assessment.

Table 2-43 Overview of all MTC events from post-marketing sources, liraglutide in WM

Product	Number of events (reporting rate [events per 1,000 PYE])	
	Serious	Non-serious
Liraglutide in WM (Saxenda®)	4 (0.002)	0 (0.000)

Background incidence and prevalence

Incidence and prevalence are largely unknown for the population of patients with T2D or obesity. Meta-analyses have indicated that obesity is associated with an increased risk of thyroid cancer, whereas an inverse association with obesity is seen for MTC.[124]

Incidence

General population: The incidence rate of MTC is observed to be 0.0021–0.0028 per 1,000 person-years.[125, 126] The age-adjusted annual incidence of MTC in the US was approximately 0.0021 per 1,000 person-years in 2012.[126] Similarly, a Danish population-based study found the age-standardised incidence of MTC to be 0.0028 per 1,000 person-years in 2014.[125]

T2D: A study from Taiwan reported incidence rates of thyroid cancer of 0.24 per 1,000 person-years among patients with T2D.[127]

Prevalence

Unknown

Risk factors and risk groups

Patient risk factors for MTC include previous family history or personal medical history of MEN2.

Preventability

No causal relationship has been established between liraglutide treatment and MTC; preventability is, therefore, not applicable.

Impact on the benefit-risk balance of the product

Based on the fact that no causal relationship was established, Novo Nordisk evaluates that the impact of consequences of ‘medullary thyroid cancer (C-cell carcinogenicity)’on the benefit–risk profile of liraglutide is low.

Public health impact

The management of MTC will impact the patient’s quality of life. Surgery is primarily required for the management of medullary thyroid cancer, but chemotherapy or radiation therapy may also be required. MTC may result in death. Due to the potential impact on the patient’s quality of life,

'medullary thyroid cancer (C-cell carcinogenicity)' is considered as an important potential risk for liraglutide in T2D and WM despite lack of established causal relationship.

Considering the extensive exposure to liraglutide in clinical studies and in post-marketing settings, the absolute risk is expected to be low and the potential impact on public health is expected to be minimal.

2.7.3.5 Important potential risk: Pancreatic cancer

Pancreatic cancer is an important potential risk for 'liraglutide inT2D' and 'liraglutide in WM'.

Potential mechanisms

Unknown

Evidence source and strength of evidence

Based on preclinical signals, an extensive review of all nonclinical and clinical study data concerning pancreatic safety was performed by the FDA and the EMA, resulting in the publication of a joint commentary in 2014[128] stating that assertions concerning a causal association between incretin-based therapies and pancreatitis or pancreatic cancer were inconsistent with the then available data.[129-131]

Patients with T2D, as well as patients with overweight or obesity, have an increased risk of certain types of cancer such as pancreatic cancer.[98, 103, 132, 133] There is currently no support from clinical studies that GLP-1-based therapies increase the risk of pancreatic cancer. However, due to the questions surrounding a potential association between GLP-1-based therapies and pancreatic cancer, pancreatic cancer has been added as a separate potential risk in line with Article 5(3) of Regulation (EC) 726/ (EMEA/H/A-5(3)/1369.

Characterisation of the risk

Frequency, seriousness and outcome

Liraglutide in T2D

CVOT EX2211-3748 (LEADER trial): Events of EAC-confirmed pancreatic neoplasms overall were identified for a few participants, and for more participants in the liraglutide group than in the placebo group (15 and 7 participants for liraglutide and placebo respectively). In both treatment groups, the majority of the EAC-confirmed pancreatic neoplasms were classified as malignant; the frequency was 0.3% (0.08 events per 100 PYO) in the liraglutide group and 0.1% (0.03 events per 100 PYO) in the placebo group (Table 2-44).

Glycaemic control studies: Three events of pancreatic neoplasms were reported in clinical studies and all were in the liraglutide treatment group. All the events were reported as serious and were assessed as unlikely related to the study product by the investigator. One of the events was associated with a fatal outcome and the other 2 events had outcome reported as 'not recovered' or 'unknown' (Table 2-45). No cases of pancreatic neoplasms were observed in the paediatric study NN2211-3659.

Overview of pancreatic cancer events in the Optum Research Database Study: Pancreatic cancer (case identification based on a pancreatic cancer algorithm)[134] was included as a secondary outcome in this study. The matched intention-to-treat analysis using Poisson regression models resulted in a rate ratio of 0.7 $[0.3;1.4]_{95\%\ CI}$ and did not suggest an elevated risk for pancreatic cancer among the liraglutide initiators relative to the cohort of all comparators.

Liraglutide in WM

Three events of pancreatic neoplasms were reported in clinical studies (1 in the liraglutide treatment group and 2 in placebo groups). Causality assessment was either missing or unlikely related to the study drug. One of the events (in placebo group) was reported with a fatal outcome. Only one event of pancreatic cancer was confirmed by an external event adjudication committee (EAC) which was reported in the liraglutide treatment group (Table 2-44). No cases of pancreatic neoplasms were observed in the paediatric studies NN8022-4180 (participants aged 12–17 years) and study NN8022-4392 (participants aged 6–12 years; Table 2-47).

Table 2-44 Overview of EAC-confirmed pancreatic neoplasm index events by malignancy status in the study EX2211-3748 (LEADER)

	Lira				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of participants	4668				4672			
PYO	17822				17741			
EAC confirmed pancreatic neoplasms	15	(0.3)	16	0.09	7	(0.1)	7	0.04
Benign	1	(0.0)	1	0.01	2	(0.0)	2	0.01
Malignant	13	(0.3)	14	0.08	5	(0.1)	5	0.03
Pre-malignant	1	(0.0)	1	0.01	0	(0.0)	0	0.00
Unclassified	0	(0.0)	0	0.00	0	(0.0)	0	0.00

N: Number of participants, E: Number of events, %: Proportion of events, R: Event rate per 100 patient years

Table 2-45 Overview of all treatment-emergent pancreatic neoplasms in exploratory/confirmatory studies − Liraglutide in T2D

	Liraglutide [1],[2]			Placebo [2]			Active comparator		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
All participants	7331			1674			3020		
Exposure (years)	4862.7			799.8			2112.2		
All pancreatic neoplasm events	3 (0.0)	3	0.6	0 (0)	0	0	0 (0)	0	0
Serious	3 (0.0)	3	0.6	0 (0)	0	0	0 (0)	0	0
Non-serious	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0
Severe	2 (0.0)	2	0.4	0 (0)	0	0	0 (0)	0	0
Moderate	1 (0.0)	1	0.2	0 (0)	0	0	0 (0)	0	0
Mild	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0
Unknown	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0
Missing	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0
Relation to study product									
Possibly/probably	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0
Unlikely	3 (0.0)	3	0.6	0 (0)	0	0	0 (0)	0	0
Missing	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0
Outcome									
Fatal	1 (0.0)	1	0.2	0 (0)	0	0	0 (0)	0	0
Recovered	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0
Recovering	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0
Recovered with sequelae	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0
Not recovered	1 (0.0)	1	0.2	0 (0)	0	0	0 (0)	0	0
Stabilised	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0
Unknown	1 (0.0)	1	0.2	0 (0)	0	0	0 (0)	0	0
Pancreatic neoplasm events leading to withdrawals	2 (0.0)	2	0.4	0 (0)	0	0	0 (0)	0	0

N: Number of participants, %: Percentage of participants, E: Number of events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 1000), MedDRA Version 22.1
[1] All liraglutide doses, [2] +/- Oral anti-diabetic add on
Relationship to study drug is based on investigator or EAC assessment.
Table only includes treatment emergent adverse events defined as adverse events occurring between first day on study product until last day on study product + 7 days (35 days for NN9535-1821).
Studies included: NN1250-3948, NN2211-1310, 1332, 1333, 1334, 1436, 1499, 1571, 1572, 1573, 1574, 1697, 1700, 1701, 1796, 1797-main, 1799, 1860-main, 1860-ext1, 2072, 3867, 3916, 3917, 3924, 3925, 3987, 4059, 4075, 4315, NN9535-1821, NN9068-3697-main-ext.
Active comparators: Oral anti diabetics, Exenatide, Glargine, Glibenclamide, Glimepiride, Insulin Degludec, Lixisenatide, Sitagliptine, Sulfonylurea.

Table 2-46 Overview of all EAC-confirmed treatment-emergent pancreatic neoplasm events in exploratory/confirmatory studies – Liraglutide in WM

	Liraglutide [1],[2]				Placebo [2]			
	N	(%)	E	R	N	(%)	E	R
All participants	3501				1843			
Years of observation	5187.6				2453.0			
All EAC confirmed pancreatic neoplasm events	1	(<0.1)	1	0.2	0			

EAC: (external) Event adjudication committee; WM: Weight management
N: Number of participants, %: Percentage of participants, E: Number of events,
R: Event rate/1,000 exposure years, MedDRA Version 19.0
[1] All liraglutide doses
[2] +/- Oral anti-diabetic add on
Table only includes treatment emergent adverse events defined as adverse events occurring between first day on study product until last day on study product + 14 days.
Studies included: NN8022-1922, 1923, 3970 and 1839 (1-year and 3-year data)

Table 2-47 Overview of all treatment emergent pancreatic neoplasms in the paediatric study with liraglutide in WM – NN8022 4392

There is no data for this table

Abbreviations: WM = weight management

Background incidence and prevalence

Incidence

T2D population: Incidence rate (IR) = 0.1–2.4 per 1,000 person-years. [98-100, 102-106, 113, 117, 135-139]

Users of GLP-1 RAs

Liraglutide users: IR = 0.20 per 1,000 person-years[140]

People who are overweight and have obesity: The incidence of pancreatic neoplasm in the females who are overweight and who have obesity, reported in the literature ranges from 0.12 to 0.34 per 1,000 person-years and from 0.15 to 0.40 per 1,000 person-years, respectively.[132, 141, 142] For men, the incidence in population with overweight and obesity is reported as 0.29 per 1,000 person-years and 0.68 per 1,000 person-years, respectively.[132]

Prevalence

Unknown

Risk factors and risk groups

Patient risk factors for neoplasm include diabetes mellitus, chronic pancreatitis, obesity, physical inactivity, advanced age, smoking, alcohol abuse, environmental factors, history of neoplasm and family history of pancreatic cancer and other genetic predisposition.

Preventability

No causal relationship has been established between liraglutide treatment and pancreatic cancer; preventability is, therefore, not applicable.

Impact on the benefit–risk balance of the product

Pancreatic cancer negatively impacts the patients' quality of life. Treatment can involve chemotherapy, radiation therapy and/or surgery. More than 50% of the patients are diagnosed at an advanced stage with a 5-year survival rate less than 5%. Due to the potential impact on the patients' quality of life, 'pancreatic cancer' is considered as an important potential risk for liraglutide in T2D and WM despite lack of established causal relationship.

However, based on the fact that no causal relationship was established, Novo Nordisk evaluates that the impact of consequences of pancreatic cancer on the benefit–risk profile of liraglutide is low for adults as well as paediatric population.

Public health impact

Considering the extensive exposure to liraglutide in clinical studies and in post-marketing settings, and the rareness of this event in the general population, the absolute risk is expected to be low and the potential impact on public health is expected to be minimal.

2.7.3.6 Missing information: Patients with a history of major depression or other severe psychiatric disorders

'Patients with a history of major depression or other severe psychiatric disorders' is considered missing information for 'liraglutide in WM'.

Evidence source

Theoretical considerations and literature.

Population in need of further characterisation

Patients with major depression and other severe psychiatric disorders were excluded from the liraglutide in weight management clinical study programme. A large proportion of patients with overweight and obesity have a history of psychiatric disorders. A meta-analysis showed patients with obesity to have a 55% increase in the risk of developing depression. In addition, depression was found to be predictive of developing obesity as 58% of individuals with clinically diagnosed depression developed obesity. Sex also appeared to play an important role as women had almost twice as high prevalence for depression as compared to men.[143] Pharmacological treatments for depression and other severe psychiatric disorders are also known to be associated with weight gain.[144]

There is currently limited information about the safety profile of liraglutide in patients being overweight and with obesity with major depression and other severe psychiatric disorders. As liraglutide has direct effect on the CNS, this population is classified as missing information for 'liraglutide in WM'.

2.7.3.7 Missing information: Concomitant use of other weight lowering products

Concomitant use of other weight-lowering products is considered missing information for 'liraglutide in WM'.

Evidence source

Theoretical considerations.

Population in need of further characterisation

Patients may receive additional products that are used for weight management. The concomitant use of other weight management drugs with liraglutide has not been studied in the clinical development programme.

There is currently limited information about the safety of using liraglutide concomitantly with other weight management therapies, and the safety of concomitant use is therefore considered missing information for 'liraglutide in WM'.

2.8 Module SVIII: Summary of safety concerns

An overview of the safety concerns for 'liraglutide in T2D' and 'liraglutide in WM' at the DLP of this RMP is provided in Table 2-48 and Table 2-49.

Table 2-48 Summary of safety concerns – Liraglutide in T2D

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	• None

Abbreviation: T2D = type 2 diabetes mellitus.

Table 2-49 Summary of safety concerns – Liraglutide in weight management

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	• Patients with a history of major depression or other severe psychiatric disorders • Concomitant use of other weight lowering products

3 Pharmacovigilance plan

3.1 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

3.1.1 Specific adverse reaction follow-up questionnaires

No specific follow-up forms or questionnaires are used for the risks associated with 'liraglutide in T2D' and 'liraglutide in WM'. Routine case follow-up includes a number of focussed questions relating to the diagnosis and description of the event. Based on medical evaluation, the relevant questions are returned to the reporter in an attempt to get further information to be used in the evaluation of the events.

3.1.2 Other forms of routine pharmacovigilance activities

No other forms of routine pharmacovigilance activities are proposed.

3.2 Additional pharmacovigilance activities

3.2.1 NN2211-3965: Medullary thyroid carcinoma surveillance study (MTC- 22341) summary

Study title: Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry

Rationale and study objectives:

This active surveillance programme will monitor any signal indicating a possible association between treatment with long-acting GLP-1 RAs and the development of MTC in the US population. The MTC registry is an FDA post-marketing requirement for long-acting GLP-1 RA products.

The objectives of this MTC Surveillance Study are:

- To systematically monitor the annual incidence of MTC in the US through North American Association of Central Cancer Registries (NAACCR) to identify any possible increase related to the introduction of long-acting GLP-1 RAs into the US market.
- To establish a registry of incident cases of MTC in adults in the US in order to characterise their medical histories and possible risk factors, including history of treatment with long-acting GLP-1 RAs.

The registry is planned to be of at least 15 years duration to systematically monitor the annual incidence of MTC in the US and to identify any increase related to the introduction of liraglutide into the marketplace.

Study design:

This active surveillance programme and case-series registry will identify incident cases of MTC that occur in targeted States in the US and evaluate the characteristics of those cases.

Cases will be identified from state/regional population-based cancer registries. Registries that have an average of at least 10 reported cases of MTC per year and meet the NAACCR standards for data collection quality and timeliness will be invited to participate in the surveillance programme. This sample will be augmented, if any of the targeted state registries refuse to participate, by adding additional state registries until the estimated, projected sample reaches at least 75% of incident cases in the US.

Case counts in the participating registries will be monitored and compared to the overall incidence to ensure the 75% sample goal is reached. An active outreach programme will be implemented to help raise awareness about the registry and to encourage inclusion of data from all incident cases of MTC in participating states.

Study populations:

Each participating registry will be asked to identify all cases of MTC in their database that were diagnosed on or after FDA approval of the first long-acting GLP-1 RA in January 2010 with the date of first MTC diagnosis. As new MTC cases are identified prospectively, each participating registry will be asked to provide report only once (avoid duplicate reporting of the same case) for each case of MTC diagnosed after 25 Jan 2010 as soon as available.

The methods for recruiting patients into the case-series registry include:

- Direct invitation of patients

In registries where direct patient contact is possible, the participating registry will be asked to send a written invitation to the patient to participate in the case series registry. The study will be explained to the patient by directly contacting them and consent to release his/her name to the study coordinating centre (SCC) will be requested. As a courtesy, the patient's physician will be notified of the case series registry study.

- Patient recruitment through the diagnosing physician

Some state or regional registries may be unable to contact a patient directly. In these situations, the patient's physician identified in the registry records will be asked to provide the required information for the case-series registry study or to recruit directly the patient for the study. The reporting registry or the SCC will send a written invitation to the physician indicating the name(s) of the patient(s) from whom information is sought. The registry will then provide the physician's name to the SCC (if not previously provided) and the SCC will follow-up with the physician to determine interest in participating in the study. If the physician agrees, he/she will be provided with a written invitation to send to the identified patient(s). The invitation will direct the patient to call the SCC and enrol in the study.

Milestones:

Planned completion of the CSR: 01 Dec 2026

3.3 Summary table of additional pharmacovigilance activities

Table 3-1 c – Liraglutide in T2D – Victoza®

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
None	N/A	N/A	N/A	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit–risk)				
None	N/A	N/A	N/A	N/A
Category 3 – Required additional pharmacovigilance activities (by the FDA)				
NN2211-3965 MTC registry (MTC-22341) Ongoing	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of liraglutide into the marketplace.	Medullary thyroid cancer	Protocol submission	28 May 2010
			Final report	01 Dec 2026

Abbreviations: FDA = U.S. Food and Drug Administration; MTC = medullary thyroid cancer; PRAC = Pharmacovigilance Risk Assessment Committee.

Table 3-2 Ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan – Liraglutide in weight management – Saxenda®

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit–risk)				
None	N/A	N/A	N/A	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit–risk)				
None	N/A	N/A	N/A	N/A
Category 3 – Required additional pharmacovigilance activities (by the FDA)				
NN2211-3965 MTC registry (MTC-22341) Ongoing	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of liraglutide into the marketplace.	Medullary thyroid cancer	Protocol submission	18 Jun 2015
			Final report	01 Dec 2026

Abbreviations: FDA = U.S. Food and Drug Administration; MTC = medullary thyroid cancer; PRAC = Pharmacovigilance Risk Assessment Committee.

4 Plans for post-authorisation efficacy studies

There are no imposed post-authorisation efficacy studies ongoing or planned for 'liraglutide in T2D' and 'liraglutide in WM'.

5 Risk minimisation measures

5.1 Routine risk minimisation measures

5.1.1 Routine risk minimisation measures – Liraglutide in T2D

Table 5-1 Description of routine risk minimisation measures by safety concern, 'Liraglutide in T2D'

Safety concern	Routine risk minimisation measures
Important potential risk Neoplasms (including melanoma)	***Routine risk communication:*** None proposed. Based on data from completed clinical studies and extensive exposure to liraglutide in the post-marketing setting, there is no indication of a relationship between treatment with liraglutide and neoplasms (including melanoma). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None
Important potential risk Medullary thyroid cancer (C-cell carcinogenicity)	***Routine risk communication:*** • Nonclinical findings are described in Section 5.3 of the SmPC. Based on data from completed clinical studies and extensive exposure to liraglutide in the post-marketing setting, there is no indication of a relationship between treatment with liraglutide and MTC. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • A warning on thyroid disease is included in Section 4.4 of the SmPC and Section 2 of the PL ***Other risk minimisation measures beyond the Product Information:*** None
Important potential risk Pancreatic cancer	***Routine risk communication:*** None proposed. Based on data from completed clinical studies and extensive exposure to liraglutide in the post-marketing setting, there is no indication of a relationship between treatment with liraglutide and pancreatic cancer. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics.

5.1.2 Routine risk minimisation measures – Liraglutide in WM

Table 5-2 Description of routine risk minimisation measures by safety concern, 'Liraglutide in WM'

Safety concern	Routine risk minimisation measures
Important potential risk Neoplasms (including melanoma)	***Routine risk communication:*** None proposed. Based on data from completed clinical studies and extensive exposure to liraglutide in the post-marketing setting, there is no indication of a relationship between treatment with liraglutide and neoplasms (including melanoma). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None
Important potential risk Medullary thyroid cancer (C-cell carcinogenicity)	***Routine risk communication:*** • Nonclinical findings are described in Section 5.3 of the SmPC. Based on data from completed clinical studies and extensive exposure to liraglutide in the post-marketing setting, there is no indication of a relationship between treatment with liraglutide and MTC. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • A warning on thyroid disease is included in Section 4.4 of the SmPC and Section 2 of the PL ***Other risk minimisation measures beyond the Product Information:*** None
Important potential risk Pancreatic cancer	***Routine risk communication:*** None proposed. Based on data from completed clinical studies and extensive exposure to liraglutide in the post-marketing setting, there is no indication of a relationship between treatment with liraglutide and pancreatic cancer. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None
Missing information Patients with a history of major depression or other severe psychiatric disorders	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None
Missing information Concomitant use of other weight lowering products	***Routine risk communication:*** • The lack of data supporting data of co-administration with other products for weight management is included in Section 4.4 of the SmPC.

Safety concern	Routine risk minimisation measures
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None proposed ***Other risk minimisation measures beyond the Product Information:*** None

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics.

5.2 Additional risk minimisation measures

No additional risk minimisation measures are planned for liraglutide in T2D and liraglutide in WM. Routine risk minimisation activities as described in Section 5.1 are sufficient to manage the safety concerns of the medicinal product.

5.3 Summary table of pharmacovigilance and risk minimisation activities by safety concern

5.3.1 Summary table of pharmacovigilance and risk minimisation activities by safety concern – Liraglutide in T2D

Table 5-3 Pharmacovigilance and risk minimisation activities by safety concern – Liraglutide in T2D

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk Neoplasms (including melanoma)	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None ***Additional risk minimisation measures*** None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities*** None
Important potential risk Medullary thyroid cancer (C-cell carcinogenicity)	***Routine risk communication:*** • Nonclinical findings are described in Section 5.3. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • A warning on thyroid disease is included in Section 4.4 of the SmPC and Section 2 of the PL ***Other risk minimisation measures beyond the Product Information:*** None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities*** NN2211-3965: MTC registry (MTC- 22341)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk Pancreatic cancer	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities*** None

Abbreviations: MTC = medullary thyroid cancer; PL = package leaflet; SmPC = Summary of Product Characteristics.

5.3.2 Summary table of pharmacovigilance and risk minimisation activities by safety concern – Liraglutide in WM

Table 5-4 Pharmacovigilance and risk minimisation activities by safety concern – Liraglutide in WM

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk Neoplasms (including melanoma)	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None ***Additional risk minimisation measures*** None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities*** None
Important potential risk Medullary thyroid cancer (C-cell carcinogenicity)	***Routine risk communication:*** • Nonclinical findings are described in Section 5.3. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:***	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:***

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• A warning on thyroid disease is included in Section 4.4 of the SmPC and Section 2 of the PL ***Other risk minimisation measures beyond the Product Information:*** None	None ***Additional pharmacovigilance activities*** NN2211-3965: MTC registry (MTC- 22341)
Important potential risk Pancreatic cancer	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities*** None
Missing information *Patients with a history of major depression or other severe psychiatric disorders*	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities*** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information Concomitant use of other weight lowering products	***Routine risk communication:*** • The lack of data supporting co-administration with other products for weight management is included in Section 4.4 of the SmPC. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities*** None

Abbreviations: MTC = medullary thyroid cancer; PL = package leaflet; SmPC = Summary of Product Characteristics.

6 Summary of the risk management plan for liraglutide

Summary of the risk management plan for Victoza (liraglutide in T2D)

This is a summary of the risk management plan (RMP) for Victoza. The RMP details important risks of Victoza, how these risks can be minimised, and how more information will be obtained about Victoza's risks and uncertainties (missing information).

Victoza's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Victoza should be used.

This summary of the RMP for Victoza should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Victoza's RMP.

6.1 The medicine and what it is used for

Victoza is authorised for the treatment of adults, adolescents and children above 10 years with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise (see SmPC for the full indication). It contains liraglutide as the active substance and it is injected subcutaneously.

Further information about the evaluation of Victoza's benefits can be found in Victoza's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: EPAR link

6.2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Victoza, together with measures to minimise such risks and the proposed studies for learning more about Victoza's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size − the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status − the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Victoza is not yet available, it is listed under 'missing information' below.

6.2.1 List of important risks and missing information

Important risks of Victoza are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Victoza. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 6-1 List of important risks and missing information

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	• None

6.2.2 Summary of important risks

Table 6-2 Important potential risk: Neoplasms (including melanoma)

Evidence for linking the risk to the medicine	Completed therapeutic confirmatory studies (phase 3a and 3b studies) in which liraglutide was used as the investigational drug and market experience until the data lock point of this report are the evidence sources of this risk. In the T2D clinical development programme, an imbalance in neoplasm reporting rates (liraglutide > comparator) was seen at the time of first marketing authorisation. The rate of malignant neoplasms was comparable between participants treated with liraglutide and those not treated with liraglutide. In the study EX2211-3748 (LEADER), similar proportions of participants in the liraglutide group and in the placebo group had neoplasms confirmed by an expert group. In the study EX2211-3748 (LEADER), the frequency of malignant melanoma confirmed by expert group was low, consistent with the rare occurrence of the disease. The numerical imbalance in the low number of patients with malignant melanoma of the skin was also reflected in a numerically higher rate of malignant melanoma observed for liraglutide (0.07 vs. 0.02 events per 100 PYO). Based on the above considerations, neoplasm (including melanoma) has been classified as an important potential risk for liraglutide in T2D.
Risk factors and risk groups	There is no indication of a causal relationship between liraglutide and the overall neoplasm. Patient risk factors for neoplasm include T2D, obesity, smoking, alcohol abuse, environmental factors, a history of neoplasm and genetic predisposition.
Risk minimisation measures	Routine risk minimisation measures *None proposed* Additional risk minimisation measures *None proposed*

Abbreviations: PYO = patient-years of observation; T2D = type 2 diabetes mellitus.

Table 6-3 Important potential risk: Medullary thyroid cancer (C-cell carcinogenicity)

Evidence for linking the risk to the medicine	Thyroid C-cell tumours were observed in liraglutide carcinogenicity studies in mice and rats. Based on mechanistic data generated by Novo Nordisk and data from the literature, it has been shown that the C-cell tumours induced in mice and rats following dosing of liraglutide are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which mice and rats are particularly sensitive, whereas monkeys and humans are not. The relevance for humans is likely to be low. Data from the intensive monitoring of calcitonin (a marker for MTC) in plasma in the liraglutide clinical development programme do not support a liraglutide effect on calcitonin in humans.
Risk factors and risk groups	There is no indication of a causal relationship between exposure to liraglutide and MTC. Patient risk factors for MTC include previous family history or personal medical history of MEN2.
Risk minimisation measures	Routine risk minimisation measures *Routine risk communication:* • *Nonclinical findings are described in Section 5.3.* *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • *A warning on thyroid disease is included in Section 4.4 of the SmPC and Section 2 of the PL* Additional risk minimisation measures *None proposed*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *NN2211-3965: MTC registry (MTC- 22341)* See Section 6.2.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: EAC = Event Adjudication Committee; MEN2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid cancer; PL = package leaflet; SmPC = Summary of Product Characteristics; SMQ = standardised MedDRA query; T2D = type 2 diabetes mellitus.

Table 6-4 Important potential risk: Pancreatic cancer

Evidence for linking the risk to the medicine	Based on preclinical signals, an extensive review of all nonclinical and clinical study data concerning pancreatic safety was performed by the FDA and the EMA, resulting in the publication of a joint commentary in 2014 stating that assertions concerning a causal association between incretin-based therapies and pancreatitis or pancreatic cancer were inconsistent with the then available data. Patients with T2D, as well as patients with overweight or obesity, have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from clinical studies that GLP-1-based therapies increase the risk of pancreatic cancer. However, due to the questions surrounding a potential association between GLP-1-based therapies and pancreatic cancer, pancreatic cancer has been added as a separate potential risk in line with Article 5(3) of Regulation (EC) 726/ (EMEA/H/A-5(3)/1369.
Risk factors and risk groups	There is no indication of a causal relationship between liraglutide and pancreatic cancer. Patient risk factors for neoplasm include diabetes mellitus, chronic pancreatitis, obesity, physical inactivity, advanced age, smoking, alcohol abuse, environmental factors, history of neoplasm and family history of pancreatic cancer and other genetic predisposition.

Risk minimisation measures	Routine risk minimisation measures *None proposed* Additional risk minimisation measures *None proposed*

Abbreviations: EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; GLP-1 = glucagon-like peptide-1; T2D = type 2 diabetes mellitus.

6.2.3 Post-authorisation development plan

6.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Victoza.

6.2.3.2 Other studies in post-authorisation development plan

NN2211-3965: MTC registry (MTC-22341)

This active surveillance programme will monitor for any signal indicating a possible association between treatment with long-acting GLP-1 RAs and the development of MTC in the US population. The MTC registry is an FDA post-marketing requirement for long-acting GLP-1 RA products.

The objectives of this MTC Surveillance Study are:

- to systematically monitor the annual incidence of MTC in the US through North American Association of Central Cancer Registries (NAACCR) to identify any possible increase related to the introduction of long-acting GLP-1 RAs into the US market
- to establish a registry of incident cases of MTC in adults in the US in order to characterise their medical histories and possible risk factors, including history of treatment with long-acting GLP-1 RAs.

Summary of the risk management plan for Saxenda (liraglutide in WM)

This is a summary of the risk management plan (RMP) for Saxenda. The RMP details important risks of Saxenda, how these risks can be minimised, and how more information will be obtained about Saxenda's risks and uncertainties (missing information).

Saxenda's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Saxenda should be used.

This summary of the RMP for Saxenda® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Saxenda's RMP.

6.3 The medicine and what it is used for

Saxenda is authorised for use as an adjunct to a reduced-calorie diet and increased physical activity for weight management in patients aged 6 years and above (see SmPC for the full indication). It contains liraglutide as the active substance and it is injected subcutaneously.

Further information about the evaluation of Saxenda's benefits can be found in Saxenda's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: EPAR link

6.4 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Saxenda, together with measures to minimise such risks and the proposed studies for learning more about Saxenda's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size − the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status − the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Saxenda is not yet available, it is listed under 'missing information' below.

6.4.1 List of important risks and missing information

Important risks of Saxenda are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Saxenda. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 6-5 List of important risks and missing information

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	• Patients with a history of major depression or other severe psychiatric disorders • Concomitant use of other weight lowering products

6.4.2 Summary of important risks

Table 6-6 Important potential risk: Neoplasms (including melanoma)

Evidence for linking the risk to the medicine	Completed therapeutic confirmatory studies (phase 3a and 3b studies) in which liraglutide was used as the investigational drug and market experience up until the data lock point of this report are the evidence sources of this risk. In the T2D clinical development programme, an imbalance in neoplasm reporting rates (liraglutide > comparator) was seen at the time of first marketing authorisation. The rate of malignant neoplasms was comparable between participants treated with liraglutide and those not treated with liraglutide. In the study EX2211-3748 (LEADER), similar proportions of participants in the liraglutide group and in the placebo group had neoplasms confirmed by an expert group. In the study EX2211-3748 (LEADER), the frequency of malignant melanoma confirmed by expert group was low, consistent with the rare occurrence of the disease. The numerical imbalance in the low number of patients with malignant melanoma of the skin was also reflected in a numerically higher rate of malignant melanoma observed for liraglutide (0.07 vs. 0.02 events per 100 PYO). No causal relationship has been established. However, based on the above considerations, neoplasm (including melanoma) has been classified as an important potential risk for liraglutide in WM.
Risk factors and risk groups	There is no indication of a causal relationship between liraglutide and the overall neoplasm. Patient risk factors for neoplasm include T2D, obesity, smoking, alcohol abuse, environmental factors, a history of neoplasm and genetic predisposition.
Risk minimisation measures	Routine risk minimisation measures *None proposed* Additional risk minimisation measures *None proposed*

Abbreviations: PYO = patient-years of observation; T2D = type 2 diabetes mellitus; WM = weight management.

Table 6-7 Important potential risk: Medullary thyroid cancer (C-cell carcinogenicity)

Evidence for linking the risk to the medicine	Thyroid C-cell tumours were observed in liraglutide carcinogenicity studies in mice and rats. Based on mechanistic data generated by Novo Nordisk and data from the literature, it has been shown that the C-cell tumours induced in mice and rats following dosing of liraglutide are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which mice and rats are particularly sensitive, whereas monkeys and humans are not. The relevance for humans is likely to be low. Data from the intensive monitoring of calcitonin (a marker for MTC) in plasma in the liraglutide clinical development programme do not support a liraglutide effect on calcitonin in humans.
Risk factors and risk groups	There is no indication of a causal relationship between exposure to liraglutide and MTC. Patient risk factors for MTC include previous family history or personal medical history of MEN2.
Risk minimisation measures	Routine risk minimisation measures *Routine risk communication:* • *Nonclinical findings are described in Section 5.3.* *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • *A warning on thyroid disease is included in Section 4.4 of the SmPC and Section 2 of the PL* Additional risk minimisation measures *None proposed*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *NN2211-3965: MTC registry (MTC- 22341)* See Section 6.4.3 of this summary for an overview of the post-authorisation development plan.

Abbreviations: GLP-1 = glucagon-like peptide-1; MEN2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid cancer; PL = package leaflet; SmPC = Summary of Product Characteristics.

Table 6-8 Important potential risk: Pancreatic cancer

Evidence for linking the risk to the medicine	Based on preclinical signals, an extensive review of all nonclinical and clinical study data concerning pancreatic safety was performed by the FDA and the EMA, resulting in the publication of a joint commentary in 2014 stating that assertions concerning a causal association between incretin-based therapies and pancreatitis or pancreatic cancer were inconsistent with the then available data. Patients with T2D, as well as patients with overweight or obesity, have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from clinical studies that GLP-1-based therapies increase the risk of pancreatic cancer. However, due to the questions surrounding a potential association between GLP-1-based therapies and pancreatic cancer, pancreatic cancer has been added as a separate potential risk in line with Article 5(3) of Regulation (EC) 726/ (EMEA/H/A-5(3)/1369.
Risk factors and risk groups	There is no indication of a causal relationship between liraglutide and pancreatic cancer. Patient risk factors for neoplasm include diabetes mellitus, chronic pancreatitis, obesity, physical inactivity, advanced age, smoking, alcohol abuse, environmental factors, history of neoplasm and family history of pancreatic cancer and other genetic predisposition.
Risk minimisation measures	Routine risk minimisation measures *None proposed*

	Additional risk minimisation measures *None proposed*

Abbreviations: EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; GLP-1 = glucagon-like peptide-1; T2D = type 2 diabetes mellitus.

Table 6-9 Missing information

Patients with a history of major depression or other severe psychiatric disorders	
Risk minimisation measures	Routine risk minimisation measures *None proposed* Additional risk minimisation measures *None proposed*
Concomitant use of other weight lowering products	
Risk minimisation measures	Routine risk minimisation measures *Routine risk communication:* • *The lack of data supporting co-administration with other products for weight management included in Section 4.4 of the SmPC* Additional risk minimisation measures *None proposed*

Abbreviations: PASS = post authorisation safety study; PL = package leaflet; SmPC = Summary of Product Characteristics.

6.4.3 Post-authorisation development plan

6.4.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Saxenda.

6.4.3.2 Other studies in post-authorisation development plan

NN2211-3965: MTC registry (MTC-22341)

This active surveillance programme will monitor for any signal indicating a possible association between treatment with long-acting GLP-1 RAs and the development of MTC in the US population. The MTC registry is an FDA post-marketing requirement for long-acting GLP-1 RA products.

The objectives of this MTC Surveillance Study are:

- to systematically monitor the annual incidence of MTC in the US through North American Association of Central Cancer Registries (NAACCR) to identify any possible increase related to the introduction of long-acting GLP-1 RAs into the US market.
- to establish a registry of incident cases of MTC in adults in the US in order to characterise their medical histories and possible risk factors, including history of treatment with long-acting GLP-1 RAs.

7 Annexes

Table 7-1 Annexes

Annex	Title	Included (Yes/No)
1	EudraVigilance interface	No
2	Tabulated summary of planned, ongoing and completed pharmacovigilance study programme	Yes
3	Protocols for proposed and ongoing studies in Categories 1–3 of the section “Summary table of additional pharmacovigilance activities” in RMP Part 3	Yes
4	Specific adverse event follow-up forms	No
5	Protocols for proposed and ongoing studies in RMP part IV	No
6	Details of proposed additional risk minimisation measures	No
7	Other supporting data (including referenced material) 7A: References	Yes
8	Summary of changes to the risk management plan over time	Yes

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