Risk Management Plan

Insulin icodec

Active substance(s)	Insulin icodec
RMP version number:	RMP version 1.0
Data lock point for this RMP	19 Sep 2022
Date of final sign off:	See signature page
Rationale for submitting an updated RMP	Not applicable, as this is the 1st RMP submitted for insulin icodec marketing authorisation application
Summary of significant changes in this RMP	Not applicable, as this is the 1st RMP submitted for insulin icodec
Other RMP versions under evaluation	None
Details of the currently approved RMP	Not applicable
QPPV	Karsten Lollike, MD, Corporate Vice President and QPPV, Global Safety
QPPV signature	See signature page

Table of contents

Page

Table of figures

Page

Table of tables

Page

Abbreviations

A1c	haemoglobin A_{1c} / HbA_{1c}
ATC	Anatomical Therapeutic Chemical
ADA	American Diabetes Association
ADR	adverse drug reaction
AE	adverse event
ASCVD	atherosclerotic cardiovascular disease
BG	blood glucose
CKD	chronic kidney disease
C_{max}	maximal binding capacity
CNS	central nervous system
CVD	chronic cardiovascular disease
CVOT	cardiovascular outcome trial
CYP450	cytochrome P450
DLP	data lock point
DPP-4i	dipeptidyl peptidase-4 inhibitor
EASD	European Association for the Study of Diabetes
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EPAR	European public assessment report
ESRD	end-stage renal disease
EU-PI	European Union product information
FHD	first human dose
FPFV	first patient first visit
GLP-1 RA	glucagon-like peptide 1 receptor agonist
HbA_{1C}	glycated haemoglobin
HF	heart failure
HFrEF	heart failure reduced ejection fraction
IB	investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICO	insulin icodec
IDEG	insulin degludec
IGLAR	insulin glargine
IMP	investigational medicinal product
IND	investigational new drug
INN	international non-propriety name
LVH	left ventricular hypertrophy
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NPH	neutral protamine Hagedorn
OAD	oral anti-diabetic drug
OD	once daily
PD	pharmacodynamic
PK	pharmacokinetic
PL	product leaflet
PT	preferred term
PYE	patient-years of exposure
rDNA	recombinant Deoxyribonucleic acid

RMP	risk management plan
RR	reporting rate
SAE	serious adverse event
s.c	subcutaneous
SGLT2i	sodium-glucose co-transporter-2 inhibitor
SmPC	Summary of Product Characteristics
SS	steady state
SU	sulfonylurea
SYE	subject-years of exposure
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
UACR	urine albumin-to-creatinine ratio

1 Product overview

Table 1-1 Product overview

Active substance(s) (INN or common name)	**insulin icodec**
Pharmacotherapeutic group(s) (ATC Code)	Insulins and analogues for injection, long-acting (A10AE06)
Marketing authorisation applicant	Novo Nordisk A/S DK-2880 Bagsværd Denmark
Medicinal products to which this RMP refers	All presentations of Awiqli® (insulin icodec)
Invented name(s) in the European Economic Area (EEA)	Awiqli® ; 700 units/mL solution for injection in pre-filled pen
Marketing authorisation procedure	EU Centralised procedure
Brief description of the product	***Chemical class:*** Insulin icodec is a long-acting basal insulin modified by the substitution of amino acid residues at A14 (tyrosine to glutamic acid), B16 (tyrosine to histidine) and B25 (phenylalanine to histidine) and the omission of two residues (B27 and B30; both threonine residues). The three amino acid substitutions enhance the stability of the insulin analogue and reduce affinity to the insulin receptor, thereby reducing clearance of the insulin analogue. Insulin icodec also contains a fatty acid side chain coupled by acylation to the amino acid backbone at the lysine residue at B29. The acylation with a long-chain fatty acid derivative facilitates a strong but reversible binding to albumin.
	Summary of mode of action: Insulin icodec is a novel long-acting insulin analogue with a long and stable pharmacodynamic (PD) and pharmacokinetic (PK) profile intended for once-weekly administration. Its molecular mode of action at the insulin receptor is the same as that of human insulin. The high binding of insulin icodec to albumin, the enzymatic stability and low affinity for the insulin receptor result in a low clearance of insulin icodec from the blood. Altogether, these properties of insulin icodec result in a low but continuous activation of the insulin receptors throughout the body over a long period of time.
	Composition: Insulin icodec is produced by the fermentation of genetically modified yeast cells (rDNA origin, *Saccharomyces cerevisiae*) followed by the attachment of an albumin-binding moiety to the purified molecule.
Hyperlink to the Product Information:	Awiqli® SmPC

Indication(s) in the EEA	**Current (if applicable)** Not applicable
	Proposed (if applicable) Awiqli® is indicated for the treatment of diabetes mellitus in adults
Dosage in the EEA	**Current (if applicable)** Not applicable
	Proposed (if applicable) This medicinal product is a basal insulin for once-weekly subcutaneous administration. It is intended to be taken on the same day of the week.
Pharmaceutical form(s) and strengths	**Current (if applicable)** Not applicable
	Proposed (if applicable) Awiqli® 700 units/mL clear, colourless, solution for injection in pre-filled pen 1 ml solution contains 700 units of insulin icodec (equivalent to 26.8 mg). Each pre-filled pen contains 700 units/mL of insulin icodec in 1, 1.5, or 3 mL volumes, respectively
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC = anatomical therapeutic chemical classification system; EEA = European Economic Area; INN = international nonproprietary name; RMP = risk minimisation plan; s.c. = subcutaneous(-ly); EU-PI = European Union product information.

2 Safety specification

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

2.1.1 Diabetes

Diabetes mellitus is a group of metabolic abnormalities leading to hyperglycaemia, which results from defects in insulin secretion, insulin action or both.[1]

Type 1 diabetes mellitus (T1D) is characterised by an autoimmune pancreatic beta-cell destruction leading to absolute insulin deficiency. People with T1D need injections of insulin every day to control the levels of glucose in their blood in order to survive.

Type 2 diabetes mellitus (T2D) is a heterogeneous, chronic, progressive disease characterised by insulin resistance, along with relatively impaired beta cell function. The course of the disease is variable but usually predictable. In the early stages, individuals with T2D have sufficient pancreatic reserves to compensate for insulin resistance and can maintain relatively normal blood glucose (BG) levels. However, over time, this ability to compensate decreases as beta-cells gradually lose their ability to secrete insulin.

2.1.1.1 Incidence and prevalence

Incidence

Overall, the incidence of T2D is greater than that of T1D. A recent study has estimated that the incidence of diabetes mellitus has globally increased by 102.9% in the period from 1990 to 2017.[2]

Type 1 diabetes mellitus

The incidence of T1D has been increasing in both children and adults; however, there are large geographical differences.[2] The highest age-structured incidence rates (per 100,000 person) in children and adolescents (age 0-14 years) were observed in North America, Western and North Europe, Saudi Arabia and Australia.[3] In European adults, age 20-59 years, the highest incidence rates were seen in Sweden, Ireland, UK, Scotland and Finland, reaching about 30 new cases per 100,000 persons per year in Sweden, Ireland and UK. In those age ≥60 years, the highest incidence rates were seen in Ireland, Sweden, Finland and Romania, reaching over 45 new cases per 100,000 persons per year in Ireland.[4] In the USA (age 20-39 years) the incidence rate varied from about 17 to about 38 new cases per 100,000 persons per year. In those aged 40-59 years and ≥60 years in the USA, the incidence rates were, respectively, about 20 and 30 new cases per 100,000 persons per year.[4] On a global level, high incidence rates were also seen in adults. For instance in Eritrea (age 20-39 years), the incidence rate was about 46 new cases per 100,000 persons per year.[4]

Type 2 diabetes mellitus

Diabetes estimates have been on the rise for several decades. More than 33% of diabetes cases were estimated to result from population growth and ageing, 28% from an increase in age-specific prevalence and 32% from the interaction of these two[5]. The incidence rates of T2D in adults range from 2.3 to 20.2 cases per 1,000 person-years with wide geographical variation[6-21]. Recent findings showed that the age-adjusted incidence rate (per 100,000 persons) was highest in Oceania (652 persons), followed by Southern sub-Saharan Africa (448 persons) and Central sub-Saharan Africa (447 persons).[2] Magliano et al. (2019) reviewed the trend in the incidence of total or T2D[22]. In the period from 2006 to 2014, the authors found an increase in the incidence of T2D in 33% (11 of 33 populations), a decreased incidence in 36% (12 of 33), and a stable incidence in 30% (10 of 33) of the evaluated separate sex specific or ethnicity specific populations. Therefore, a variable trend in the incidence of T2D was observed.

Prevalence

In 2021, the estimated crude prevalence of diabetes in adults aged 20–79 years was 10.5% globally (the vast majority of cases being T2D).[3] The age-adjusted prevalence varied from one region to another with the highest prevalence in the Middle East and North Africa (16.2%) followed by North America and Caribbean (14%).[3] The lowest prevalence is in Africa (4.5%) followed by South East Asia (8.7%).[3] For Europe, the age-adjusted prevalence of diabetes was 9.2%, in general.[3] Turkey (15.9%), Spain (14.8), Andorra (13.9) and Portugal (13%) have the highest crude prevalence, and Ireland (4%) and Greenland (4.5%) have the lowest crude prevalence of diabetes[3]. At the global level, Pakistan (30.8%), French Polynesia (25.2) and Kuwait (24.9) have the highest age-adjusted prevalence of diabetes.[3]

From 1990 to 2017, large increase in the age adjusted prevalence rates of diabetes were observed, reaching up to 39.2% in North America and Western sub-Saharan Africa.[2] For T1D, the largest increase (28%) in the age-adjusted prevalence rate was observed in Western Europe, while a decrease by 0.2% was observed in South Asia.[2] For T2D, the highest increase was observed in North America (42.6%), while a decrease by 5.7% was observed in Australasia.[2]

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

Type 1 diabetes mellitus

T1D is the predominant type of diabetes in childhood and adolescence, accounting for >90% of all diabetes cases in white youth aged less than 20 years [9, 23].In most populations, T1D incidence rates rise from infancy and peak between the ages of 10 and 14 years during puberty.[24] The majority develop the disease before the age of 30 years, with incidence rates declining after puberty[25-27] and stabilising in young adulthood (15–29 years).[28] Nevertheless, a recent systematic review of adult onset T1D, has shown that high incidence of T1D can be seen in adults, reaching over 45 new cases per 100,000 persons per year[4], indicating the need for more attention to T1D onset in adults. In the USA, a study on the incidence of T1D showed a generally stable incidence rate in adults from 2001 to 2015. Nevertheless, an upward trend in the incidence starting at age 40 was observed[29].

A systematic review showed that adult onset T1D incidence were highest in north European populations, but comparable incidence were also seen in low income countries such as Eritrea[4]. This demonstrates a substantial burden of adult onset T1D incidence and the need for more information on its occurrence and characteristics. For age groups older than 15 years, prevalence [30] and incidence [9, 31] of T1D are higher among males than females. Roger et al. showed a male to female incidence rate ratio of 1.32 in the USA[29]. Clinical presentation of T1D may occur at any age[9].

Type 2 diabetes mellitus

T2D usually occurs in adults but is increasingly seen in children and adolescents.[33] The prevalence[3] and incidence[11] of T2D become progressively higher with advancing age. The incidence[9, 11-12, 14] and prevalence[32] of T2D tend to be a little higher in males than in females. In the US, the incidence[21] and prevalence[33] of T2D is lower in whites than other ethnic groups. The prevalence is highest in African Americans[33] and the incidence is highest in Pacific Islanders and South Asians [21]. In the USA from 2002 to 2012, the highest annual increase in the incidence rate of T2D was observed among native Americans (8.9%) followed by Pacific Islander (8.5%), while the lowest increase was observed among non-Hispanic whites (0.6%)[34].

2.1.1.3 Risk factors for the disease

Type 1 diabetes mellitus

T1D is heritable with both genetic[35-36] and environmental factors[37] potentially playing a role. Reasons for the increasing number of people who develop T1D remain unclear.

Type 2 diabetes mellitus

Although the exact causes for the development of T2D are unknown, there are several known risk factors. The most important risk factors are excess body weight (overweight and obesity), physical inactivity, dietary factors and genetics.[3] Additional risk factors include smoking, impaired glucose tolerance, abnormal lipids, hypertension, inflammation, increasing age, male gender, ethnic and genetic pre-disposition, history of gestational diabetes and polycystic ovary syndrome.

2.1.1.4 The main existing treatment options

Type 1 diabetes mellitus

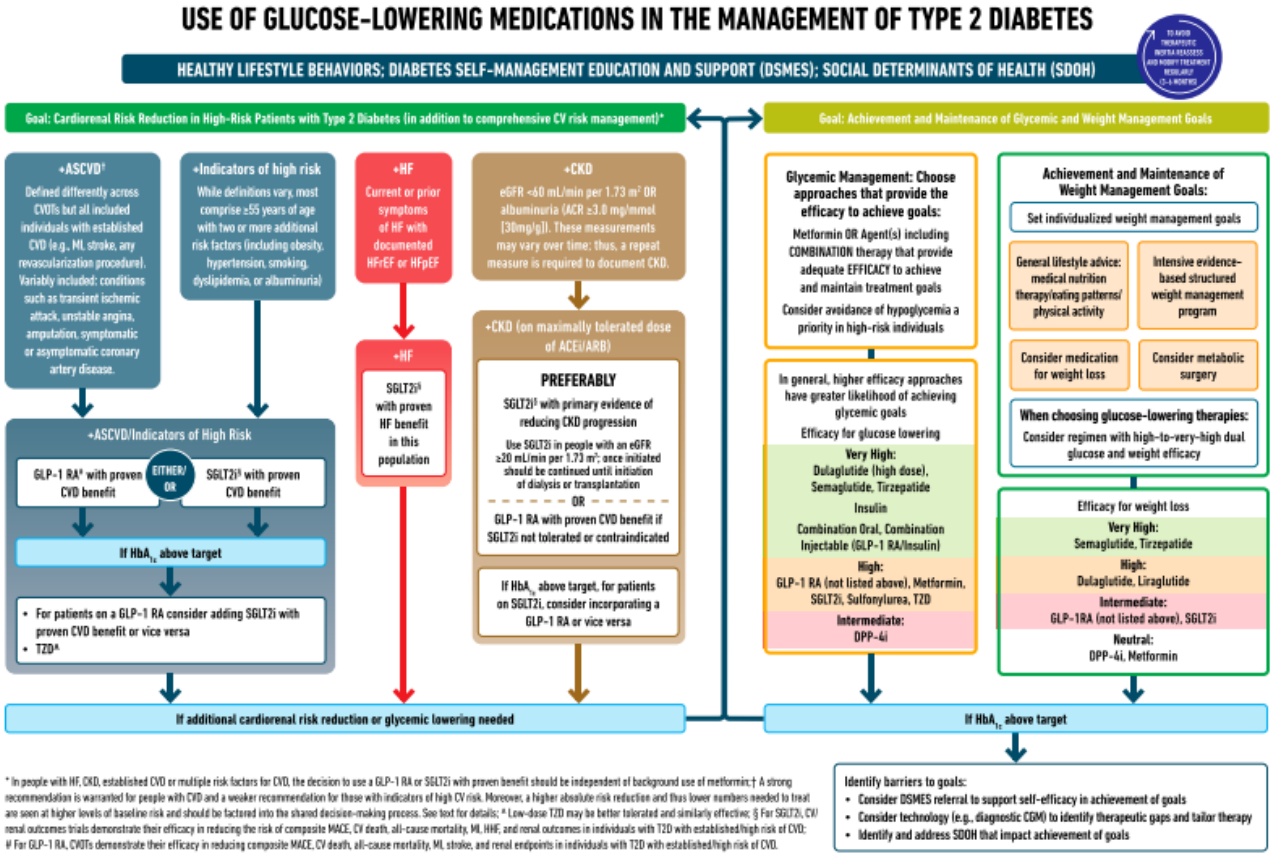
For people with T1D, treatment typically includes a carefully calculated diet, planned physical activity, and home blood glucose (BG) testing several times a day accompanied by multiple daily insulin injections. Although diet and exercise are important in the treatment of T1D, they do not reverse the disease or remove the need for insulin.

Technological advancement during the past years made available insulin pumps, continuous glucose monitoring and systems that combine both insulin pumps and a monitor for algorithm-driven automation of insulin delivery[38]. Although of limited application, treatment of T1D via Islet or Pancreas transplantation is available[39].

Type 2 diabetes mellitus

A hierarchy of the available treatment options for T2D as recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) is presented in Figure 2-1.

Figure 2-1 Glucose-lowering medication in type 2 diabetes: overall approach[40]



Abbreviations: ASCVD = atherosclerotic cardiovascular disease; A_{1C} = haemoglobin A_{1c} / HbA_{1c}; CKD = chronic kidney disease; CVD = cardiovascular disease; CVOT = cardiovascular outcomes trial; DPP-4i = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; HFrEF = heart failure reduced ejection fraction; LVH = left ventricular hypertrophy; LVEF = left ventricular ejection fraction; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione; UACR = urine albumin-to-creatinine ratio.

2.1.1.5 Natural history of the indicated condition including mortality and morbidity

Type 1 diabetes mellitus

The natural history of T1D is initiation of β-cell autoimmunity that eventually may destroy all β cells, resulting in a progressive and predicable loss in insulin secretory function. T1D does not present until the majority of the β-cells are destroyed as there is a gap between the onset of autoimmunity and the onset of diabetes.[41] T1D can affect major organs in the body, including heart, blood vessels, nerves, eyes, and kidneys, mainly due to hyperglycaemia. These long-term complications can develop gradually and may eventually be disabling or even life-threatening.

In many countries worldwide, excess mortality has been observed in subjects with T1D diagnosed in childhood and adolescence compared with the general population, with lower excesses mortality in more recent European studies and higher excesses mortality in earlier studies from Cuba, Lithuania and the US.[42]

Women with T1D have a nearly 40% greater risk of all-cause mortality compared with men with T1D.[43] For macrovascular outcomes (including cardiovascular and renal diseases), the excess risk of mortality in women compared with men was even more extreme (44% for fatal renal disease, and 86% for fatal cardiovascular diseases).[43]

Type 2 diabetes mellitus

T2D is a heterogeneous, chronic and progressive disease characterised by insulin resistance (response to insulin to the target tissues, such as muscle, liver and adipose tissue), along with relatively impaired beta-cell function. The disease 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), eventually leading to state of insulin dependency.[44]

The endpoint of the disease process, insulin deficiency, can be absolute or relative in the coexistence of insulin resistance. 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.[44-46]

T2D is associated with increased all-cause mortality.[47] Cardiovascular disease is a major cause of death in patients with T2D[48]. Furthermore, cancer patients with diabetes have poorer survival chances and higher cancer mortality rates than cancer patients without diabetes,[49-50] particularly so for liver, pancreatic, ovary and colorectal cancer.[51]

2.1.1.6 Important co-morbidities found in the target population

People with diabetes are at a higher risk of developing a number of disabling and life-threatening health problems than people without diabetes.[5] Persistent hyperglycaemia may lead to the development of microvascular pathology in the retina, renal glomerulus and peripheral nerve.[52] 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. The important co-morbidities found in the target population are presented in Table 2-1.

Table 2-1 Important co-morbidities found in the target population

Important co-morbidity category	Important co-morbidity sub-category
Macrovascular complications	• Congestive heart failure • Myocardial infarction • Peripheral arterial disease • Stroke
Microvascular complications	• Chronic kidney disease and nephropathy • Peripheral neuropathy • Retinopathy • Extremity ulcers • Autonomic neuropathy
Cancer	• Overall cancer • Liver • Pancreatic • Colorectal
Acute complications	• Diabetic ketoacidosis • Hyperosmolar hyperglycaemic state
Other	• Hypertension • Dyslipidaemia • Pancreatitis • Obesity

2.2 Module SII: Non-clinical safety findings

2.2.1 Important nonclinical safety findings and their relevance to human use

A summary of important nonclinical findings is presented, along with assessments of the human relevance, in Table 2-2.

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

Key safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
General toxicity studies Hypoglycaemia From repeated-dose toxicity studies (subcutaneous administration) in Sprague Dawley rats and the Beagle dogs, clinical signs of hypoglycaemia and hypoglycaemia-related mortality was reported. In several studies, the dose levels of insulin icodec had to be reduced during the study course due to clinical signs of hypoglycaemia and hypoglycaemia-related mortality Dosing of healthy normo-glycaemic animals with insulin lowers BG to levels below the normal range. Depending on the magnitude and duration of the BG lowering, this may lead to clinical signs of hypoglycaemia and subsequent effects such as increased food consumption, metabolic changes in clinical chemistry. In some cases, sciatic nerve degeneration and associated atrophy/necrosis of skeletal muscle or even hypoglycaemia-related mortality have been observed in rats. These effects when dosing normo-glycaemic animals are a result of the inherent pharmacological action of insulin and are therefore considered representing intended or exaggerated pharmacology rather than toxicity.	Hypoglycaemia was seen in nonclinical studies and is a result of the PD properties of the insulin product. Severe hypoglycaemia may result in a fatal outcome.
Reproductive toxicity Insulin icodec had no signs of maternal toxicity and no effects on fertility, embryo-foetal survival, pre- or post-implantation loss, placental weight, foetal weight or sex ratio were observed as result of insulin icodec exposure. At all dose levels in rats and rabbits, there were no major and minor visceral or skeletal abnormalities that show a relationship to dosing with insulin icodec. During lactation, maternal toxicity related to hypoglycaemia was observed, leading to underfeeding of the pups and subsequent clinical signs and mortality among the pups.	All effects were considered secondary changes to the effect on the maternal blood glucose levels (hypoglycaemia), and without toxicological significance.
Carcinogenicity studies The potential carcinogenic effect of insulin icodec was evaluated in the 52-week rat study. Dosing with insulin icodec was not associated with hyperplastic findings or tumour development. Specifically, the incidence of mammary gland hyperplastic findings and tumours in females was similar between all groups including the control group.	Based on a comprehensive *in vitro* and *in vivo* evaluation, the carcinogenic potential of insulin icodec was found to be similar to that of human insulin.

Key safety findings (from nonclinical studies)	Relevance to human usage
Insulin icodec did not induce in vitro genotoxicity as tested by Ames screening test. Further, the linker spacer structure when evaluated in the Derek Nexus System did not raise any alerts for carcinogenicity, chromosome damage, genotoxicity, or mutagenicity.	
Mitogenicity studies The *in vitro* mitogenic/metabolic potency ratio for insulin icodec is similar to that of human insulin.	Studies support that the balance between the metabolic and proliferative actions is similar to that of human insulin.
Immunogenicity Formation of antibodies towards insulin icodec was seen in the 8- and 26-week repeated dose toxicity studies in rats and dogs. Based on evaluation of the glucose lowering effect of insulin icodec and exposure, the antibodies are not considered to have influenced the study outcome.	Antibody formation against insulin icodec could result in lack of efficacy. Antibody formation in animals is not considered predictive for humans.
Injection site tolerability Local tissue reactions were mild and similar to those of the vehicle or NPH insulin. After repeated dose administration in minipig, rat and dog, the local reaction was comparable between vehicle control and insulin icodec dosed groups. Thus, the reaction at the s.c. injection sites is considered related to the injection procedure rather than insulin icodec itself.	No safety concerns were raised.
General safety pharmacology Insulin icodec was well tolerated in safety pharmacology studies assessing cardiovascular, respiratory and CNS functions. There were no findings at single s.c. doses up to and including 150 nmol/kg in the rat and 21 nmol/kg in the dog.	No safety concerns were raised.
Mechanisms for drug interactions Insulin icodec showed low potential for drug–drug interactions in the nonclinical studies. A minor increase in liver CYP450 enzymes was observed after insulin icodec treatment in the rat, however with no clear dose-response. It was concluded that insulin icodec treatment had only minor impact on regulation of CYP450 enzymes, and the effect was considered to have no clinical relevance. Plasma protein binding studies showed that insulin icodec was highly bound with over 99% binding in humans. The competitive displacement of albumin bound insulin icodec by other drugs is considered unlikely due to the high concentration of albumin in serum (~0.6 mM or 600.000 nM) in comparison to insulin icodec in human serum (C_{max} = 266 nM). Hence, the albumin concentration will be >2000-fold higher than that of insulin icodec.	No safety concerns were raised.

Key safety findings (from nonclinical studies)	Relevance to human usage
Other toxicity-related information or data No information is available.	None.

Abbreviations: BG = blood glucose; C_{max} = maximal binding capacity; CNS = central nervous system; CYP450 = cytochrome P450; NPH = neutral-protamine-Hagedorn; PD = pharmacodynamics.

2.2.2 Conclusions on nonclinical data

Based on the evaluation of nonclinical data, the risk related to hypoglycaemia was deemed to be relevant to humans, however it was well-characterised and adequately managed through routine pharmacovigilance and risk minimisation activities. Therefore, the risk of 'Hypoglycaemia' has not been included in the list of safety concerns (see Table 2-3).

Table 2-3 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) • None
Important missing information • None

2.3 Module SIII: Clinical trial exposure

2.3.1 Overall clinical experience with insulin icodec

The clinical development programme for insulin icodec was initiated in 2016. Insulin icodec is a novel long-acting insulin analogue, which has been developed to safely cover the basal insulin requirements for a full week with a single subcutaneous (s.c.) injection. The clinical development programme was designed to characterise the pharmacokinetic (PK) and pharmacodynamic (PD) properties of insulin icodec and to confirm the efficacy and safety of once-weekly dosing of insulin icodec in adult subjects with diabetes who can benefit from insulin therapy. Thus, insulin icodec was studied alone or in combination with OADs (including metformin, sulfonylureas, glinides, GLP-1 receptor agonists, dpp-4 inhibitors and SGLT2 inhibitors) and/or meal-time insulin (insulin aspart [IAsp]) for either insulin initiation or insulin intensification in adult subjects with T1D or T2D. The comparators used in the insulin icodec clinical programme included insulin glargine (IGlar; U100 and U300) and insulin degludec (IDeg).

As of 19 Sep 2022, insulin icodec has been administered in 18 completed clinical trials encompassing phase 1 (9 trials), phase 2 (3 trials), and phase 3a (6 trials) (see Table 2-4).

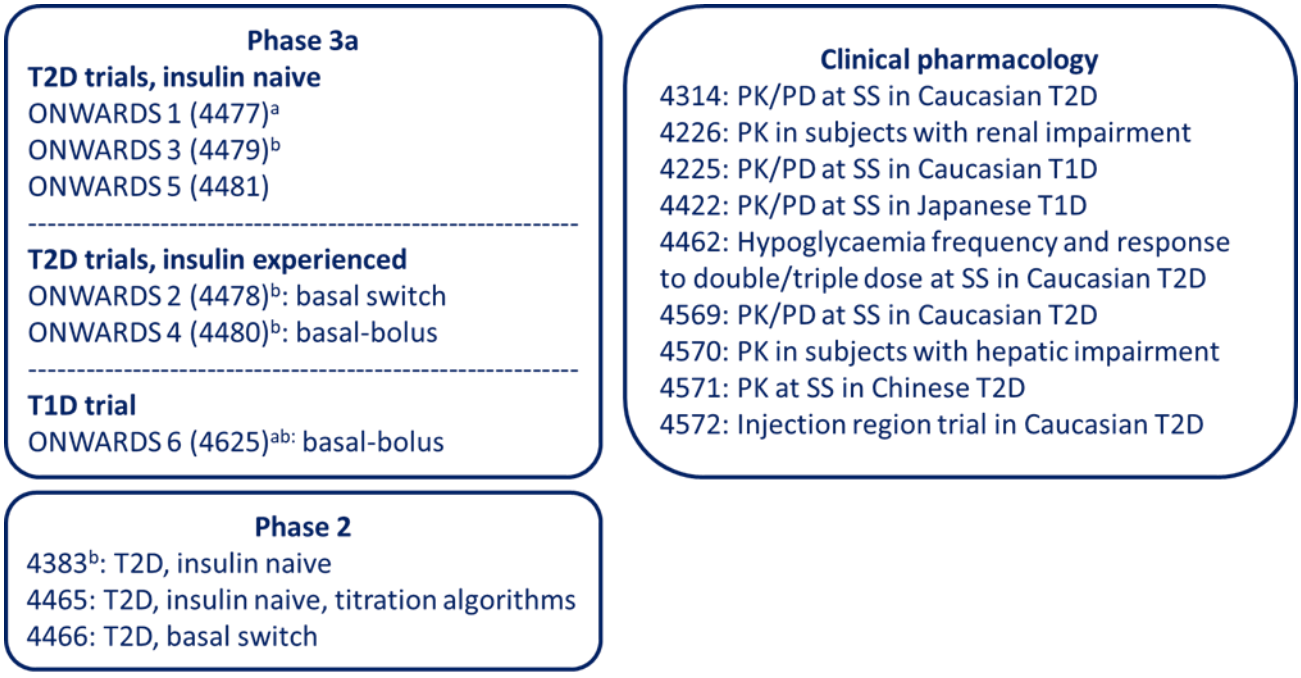
Table 2-4 Summary tabulation of insulin icodec clincal study programme by study ID, phase, and study description

Study ID	Phase	Study Description
NN1436-4225	Phase 1	A study investigating the pharmacokinetics and pharmacodynamics of insulin icodec at steady state conditions in study subjects with T1D
NN1436-4226		Investigation of pharmacokinetics and safety profile of a single dose insulin icodec in study subjects with various degrees of renal impairment
NN1436-4314		A multiple dose study investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of insulin icodec for subcutaneous administration in study subjects with T2D.
NN1436-4422		A multiple-dose trial investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of insulin icodec for subcutaneous administration in Japanese subjects with T1D.
NN1436-4462		A study investigating the hypoglycaemic response to overdosing of insulin icodec in study subjects with T2D
NN1436-4569		A study investigating the pharmacokinetic and pharmacodynamic properties of insulin icodec in study subjects with T2D.
NN1436-4570		A study investigating the pharmacokinetic properties of insulin icodec in study subjects with various degrees of hepatic impairment.
NN1436-4571		A study investigating the pharmacokinetic properties of insulin icodec in Chinese study subjects with T2D.
NN1436-4572		A study investigating the pharmacokinetic properties of insulin icodec after administration in different injection regions in trial subjects with T2D.
NN1436-4383	Phase 2	An investigational study comparing the efficacy and safety of once weekly insulin icodec versus once daily insulin glargine, both in combination with metformin, with or without DPP4 inhibitors, in insulin naïve subjects with T2D.
NN1436-4465		A study comparing insulin icodec versus insulin glargine, both in combination with metformin, with or without DPP4 inhibitors and with or without SGLT2 inhibitors, in insulin-naïve study subjects with T2D.
NN1436-4466		A study comparing insulin icodec versus insulin glargine, both in combination with metformin, with or without DPP4 inhibitors and with or without SGLT2 inhibitors, in basal insulin treated study subjects with type 2 diabetes mellitus
NN1436-4477	Phase 3a	A study comparing the effect and safety of once weekly insulin icodec and once daily insulin glargine, both in combination with non-insulin anti diabetic treatment, in insulin naïve study subjects with T2D (ONWARDS 1 – main part).
NN1436-4478		A study comparing the effect and safety of once weekly insulin icodec and once daily insulin degludec, both with or without non-insulin anti-diabetic drugs, in study subjects with T2D treated with basal insulin (ONWARDS 2)

Study ID	Phase	Study Description
NN1436-4479		A double blinded, multiregional, study comparing the effect and safety of once weekly insulin icodec and once daily insulin degludec, both in combination with non-insulin anti-diabetic drugs, in insulin naïve study subjects with T2D (ONWARDS 3)
NN1436-4480		A study comparing the effect and safety of once weekly insulin icodec and once daily insulin glargine, both in combination with bolus insulin with or without non-insulin anti-diabetic drugs, in study subjects with T2D on a basal-bolus regimen (ONWARDS 4)
NN1436-4481		Effectiveness and safety of once weekly insulin icodec with Doseguide versus basal insulin analogues in an insulin naïve T2D population in a clinical practice setting (ONWARDS 5)
NN1436-4625		Efficacy and safety of once weekly insulin icodec compared to once daily insulin degludec, both in combination with insulin aspart, in adults with type 1 diabetes (ONWARDS 6 - main part)

Abbreviation: DPP4 = dipeptidyl peptidase-4; SGLT2 = sodium-glucose transporter protein 2; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus.

Figure 2-2 Overview of clinical development programme



[a]Data from main part of trial included in the application. [b] Trial data included in population pharmacokinetics assessment.

Abbreviations: T1D = type 1 diabetes; T2D = type 2 diabetes ; PK = pharmacokinetics; PD = pharmacodynamics; statistically significant = steady state

The clinical pharmacology (phase 1) component of the programme evaluated PK and PD data in trial subjects with T2D (NN1436-4134, -4569, -4571, and -4572), T1D (NN1436-4225, and -4422), as well as subjects with varying degrees of renal (NN1436-4226) and hepatic (NN1436-4570) impairment. While the majority of studies involved subjects from Europe (Germany, Austria, Czech

Republic, and Slovakia), 2 studies (NN1436-4422 [Japan] and NN1436-4571 [China]) also evaluated the pharmacokinetic characteristics of insulin icodec in Asian populations.

Phase 2 trials with insulin icodec as the primary investigational medicinal product have been conducted comparing the safety and efficacy of insulin icodec, as compared to the once-daily basal insulin insulin glargine U100, in trial subjects with T2D. Trial design considered both insulin-naïve (NN1436-4383 and -4465) subjects as well as subjects switching to a once-weekly basal insulin from a once-daily regimen (NN1436-4466). Titration algorithms for dosing regimens with insulin icodec were evaluated for both naïve subjects (NN1436-4465) and subjects previously administering once-daily insulin therapy (NN1436-4466).

The phase 3a programme evaluated the safety and efficacy of once-weekly dosing regimens with insulin icodec as compared with once-daily regimens (IGlar, U100 and U300, or IDeg, 100 U/mL) concerning subjects with T1D (NN1436-4625) or T2D (all other phase 3a trials). Notably, phase 3a trial design accounted for co-administration of OADs (NN1436-4477 and -4479), usage of a bolus insulin (NN1436-4480 and -4625) switching from other basal insulins (NN1436-4478) and the incorporation a supportive self-titration guidance app in a clinical practice setting (NN1436-4481).

While exposure data is an aggregate of the entire clinical trial programme, the safety evaluation is based mainly on data from six randomised multiple dose clinical trials, NN1436-4477, - 4478, - 4479, -4480, -4481, and -4625 with exposure presented in Section 2.3.1.1 (cut-off date 19 Sep 2022).

2.3.1.1 Clinical exposure to insulin icodec in randomised clinical trials

Cumulatively, until 19 Sep 2022, a total of 5,307 study subjects were exposed to insulin icodec, comparators or placebo. 52.8 % of the subjects were exposed to insulin icodec compared to 47.2% exposed to comparators or placebo; see Table 2-6. Subjects with T1D were exposed to insulin icodec for up to 6 months and subjects with T2D were exposed to insulin icodec for up to 12 months; see Table 2-5 and Figure 2-3.

Of those exposed to insulin icodec, the majority (69.3%) of study subjects were adults (18-64 years of age), with additional elderly subpopulations including subjects between 65 and 75 years of age (27.2% of subjects) and those over 75 years of age (3.6%). The distribution of subject gender for those treated with insulin icodec was slightly weighted towards males (60:40 male:female ratio); see Table 2-7. Approximately 76 % of the study subjects treated with insulin icodec were White; see Table 2-8.

The demographic composition of the subjects exposed to comparators was similar to that for insulin icodec-treated subjects.

Table 2-5 Duration of exposure

Product	Population/ Indication	Duration	Ico	Comparator	Total
			N	N	N
insulin icodec	T1DM	>00 months	290	292	582
		>01 months	288	291	579
		>02 months	287	287	574
		>03 months	284	287	571
		>04 months	281	285	566
		>05 months	277	284	561
		>06 months	227	228	455
	T2DM	>00 months	2263	2101	4364
		>01 months	2250	2088	4338
		>02 months	2239	2065	4304
		>03 months	2231	2055	4286
		>04 months	2217	2049	4266
		>05 months	1953	1936	3889
		>06 months	1932	1925	3857
		>07 months	1889	1885	3774
		>08 months	985	993	1978
		>09 months	981	987	1968
		>10 months	974	986	1960
		>11 months	972	982	1954
		>12 months	614	643	1257
		>13 months	350	374	724
		>14 months	2	4	6
	All subjects	>00 months	2553	2393	4946
		>01 months	2538	2379	4917
		>02 months	2526	2352	4878
		>03 months	2515	2342	4857
		>04 months	2498	2334	4832
		>05 months	2230	2220	4450
		>06 months	2159	2153	4312
		>07 months	1889	1885	3774

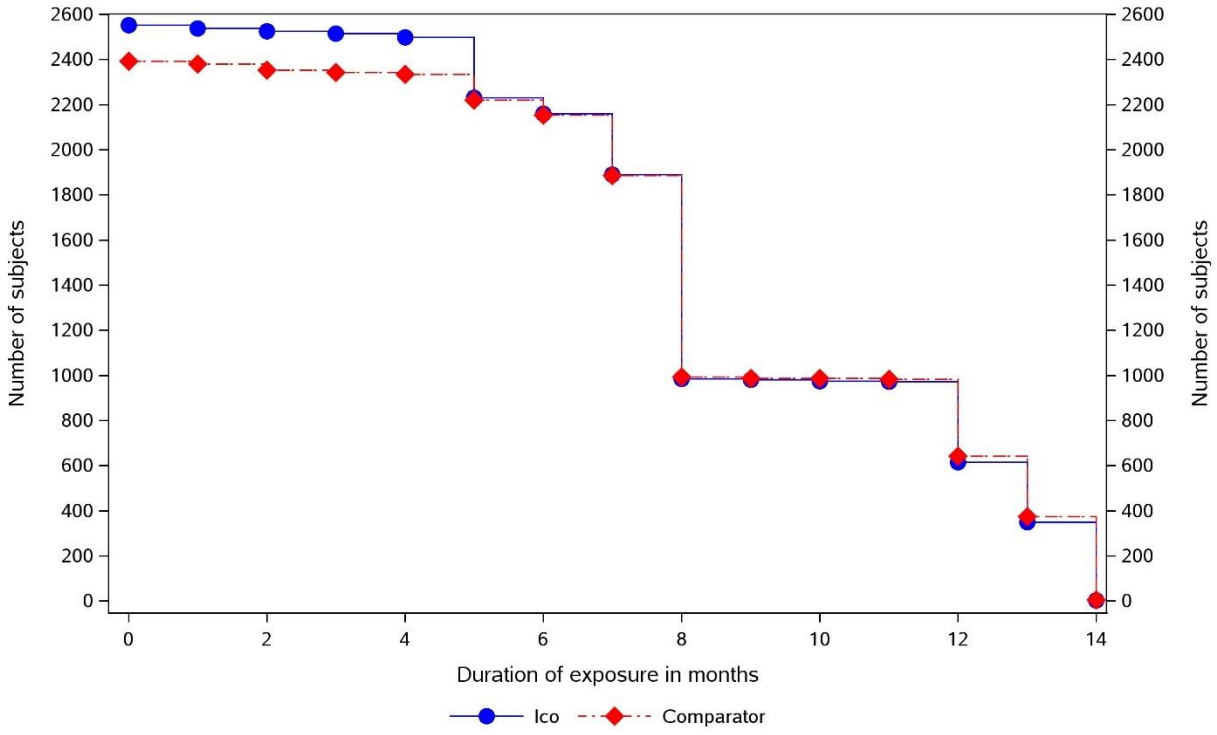
N: Number of subjects
Exploratory/confirmatory trials included: nn1436-4383, nn1436-4466, nn1436-4465, NN1436-4480, NN1436-4479, NN1436-4625, NN1436-4477, NN1436-4481, NN1436-4478
One month is defined as 365.25/12 (~30.4) days.; Comparator: IGlar, IDeg, OD analogues

Product	Population/ Indication	Duration	Ico N	Comparator N	Total N
insulin icodec	All subjects	>08 months	985	993	1978
		>09 months	981	987	1968
		>10 months	974	986	1960
		>11 months	972	982	1954
		>12 months	614	643	1257
		>13 months	350	374	724
		>14 months	2	4	6

N: Number of subjects
Exploratory/confirmatory trials included: nn1436-4383, nn1436-4466, nn1436-4465, NN1436-4480, NN1436-4479, NN1436-4625, NN1436-4477, NN1436-4481, NN1436-4478
One month is defined as 365.25/12 (~30.4) days.
Comparator: IGlar, IDeg, OD analogues

Abbreviations: Ico = insulin icodec, IDeg = insulin degludec; IGlar = insulin glargine; OD = once daily.

Figure 2-3 Number of subjects by duration of exposure to insulin icodec and comparators in months in completed exploratory and confirmatory trials



Abbreviations: Ico = insulin icodec.

Table 2-6 Total cumulative exposure to insulin icodec and comparators in completed clinical trials by indication, population, category and treatment

Product	Population/ Indication	Treatment	Number of subjects (%)	SYE
Clinical Pharmacology trials				
	Hepatic Impairment	Ico	25 (6.9)	NA
		Total	25 (6.9)	NA
	Renal Impairment	Ico	58 (16.1)	NA
		Total	58 (16.1)	NA
	T1DM	Ico	45 (12.5)	NA
		Comparator	45 (12.5)	NA
		Total	90 (24.9)	NA
	T2DM	Ico	154 (42.7)	NA
		Comparator	34 (9.4)	NA
		Total	188 (52.1)	NA
	All subjects	Ico	282 (78.1)	NA
		Comparator	79 (21.9)	NA
		Total	361 (100.0)	NA

SYE: Subject years of exposure
Clinical pharmacology trials included: nn1436-4226, nn1436-4422, nn1436-4314, nn1436-4225, nn1436-4462, nn1436-4570, nn1436-4572, nn1436-4571, nn1436-4569
Exploratory/confirmatory trials included: nn1436-4383, nn1436-4466, nn1436-4465, NN1436-4480, NN1436-4479, NN1436-4625, NN1436-4477, NN1436-4481, NN1436-4478
Comparator: IGlar, IDeg, OD analogues

Abbreviations: Ico = insulin icodec, IDeg = insulin degludec; IGlar = insulin glargine; OD = once daily.

Product	Population/ Indication	Treatment	Number of subjects (%)	SYE
Exploratory/confirmatory clinical trials				
	T1DM	Ico	290 (5.9)	142.3
		Comparator	292 (5.9)	144.1
		Total	582 (11.8)	286.4
	T2DM	Ico	2263 (45.8)	1715.5
		Comparator	2101 (42.5)	1647.4
		Total	4364 (88.2)	3362.8
	All subjects	Ico	2553 (51.6)	1857.8
		Comparator	2393 (48.4)	1791.5
		Total	4946 (100.0)	3649.3

SYE: Subject years of exposure
Clinical pharmacology trials included: nn1436-4226, nn1436-4422, nn1436-4314, nn1436-4225, nn1436-4462, nn1436-4570, nn1436-4572, nn1436-4571, nn1436-4569
Exploratory/confirmatory trials included: nn1436-4383, nn1436-4466, nn1436-4465, NN1436-4480, NN1436-4479, NN1436-4625, NN1436-4477, NN1436-4481, NN1436-4478
Comparator: IGlar, IDeg, OD analogues

Abbreviations: Ico = insulin icodec, IDeg = insulin degludec; IGlar = insulin glargine; OD = once daily.

Product	Population/ Indication	Treatment	Number of subjects (%)	SYE
All trials				
	Hepatic Impairment	Ico	25 (0.5)	
		Total	25 (0.5)	
	Renal Impairment	Ico	58 (1.1)	
		Total	58 (1.1)	
	T1DM	Ico	335 (6.3)	
		Comparator	337 (6.4)	
		Total	672 (12.7)	
	T2DM	Ico	2417 (45.5)	
		Comparator	2135 (40.2)	
		Total	4552 (85.8)	
	All subjects	Ico	2835 (53.4)	
		Comparator	2472 (46.6)	
		Total	5307 (100.0)	

SYE: Subject years of exposure
Clinical pharmacology trials included: nn1436-4226, nn1436-4422, nn1436-4314, nn1436-4225, nn1436-4462, nn1436-4570, nn1436-4572, nn1436-4571, nn1436-4569
Exploratory/confirmatory trials included: nn1436-4383, nn1436-4466, nn1436-4465, NN1436-4480, NN1436-4479, NN1436-4625, NN1436-4477, NN1436-4481, NN1436-4478
Comparator: IGlar, IDeg, OD analogues

Abbreviations: Ico = insulin icodec, IDeg = insulin degludec; IGlar = insulin glargine; OD = once daily.

Table 2-7 Total exposure by indication, age group and gender

Product	Age range	Ico N (%)			Comparator N (%)		
		Male	Female	Total	Male	Female	Total
Clinical Pharmacology trials							
Hepatic Impairment	18<= to <65 years	10 (2.8)	10 (2.8)	20 (5.5)	0	0	0
	65<= to <75 years	2 (0.6)	3 (0.8)	5 (1.4)	0	0	0
	Total	12 (3.3)	13 (3.6)	25 (6.9)	0	0	0
Renal Impairment	18<= to <65 years	32 (8.9)	16 (4.4)	48 (13.3)	0	0	0
	65<= to <75 years	7 (1.9)	3 (0.8)	10 (2.8)	0	0	0
	Total	39 (10.8)	19 (5.3)	58 (16.1)	0	0	0
T1DM	18<= to <65 years	33 (9.1)	12 (3.3)	45 (12.5)	37 (10.2)	8 (2.2)	45 (12.5)
	Total	33 (9.1)	12 (3.3)	45 (12.5)	37 (10.2)	8 (2.2)	45 (12.5)
T2DM	18<= to <65 years	94 (26.0)	31 (8.6)	125 (34.6)	19 (5.3)	8 (2.2)	27 (7.5)
	65<= to <75 years	24 (6.6)	5 (1.4)	29 (8.0)	6 (1.7)	1 (0.3)	7 (1.9)
	Total	118 (32.7)	36 (10.0)	154 (42.7)	25 (6.9)	9 (2.5)	34 (9.4)
All subjects	18<= to <65 years	169 (46.8)	69 (19.1)	238 (65.9)	56 (15.5)	16 (4.4)	72 (19.9)
	65<= to <75 years	33 (9.1)	11 (3.0)	44 (12.2)	6 (1.7)	1 (0.3)	7 (1.9)
	Total	202 (56.0)	80 (22.2)	282 (78.1)	62 (17.2)	17 (4.7)	79 (21.9)
Exploratory/confirmatory clinical trials							
T1DM	18<= to <65 years	146 (3.0)	121 (2.4)	267 (5.4)	160 (3.2)	111 (2.2)	271 (5.5)
	65<= to <75 years	17 (0.3)	3 (0.1)	20 (0.4)	9 (0.2)	9 (0.2)	18 (0.4)
	Elderly (75<= years)	2 (0.0)	1 (0.0)	3 (0.1)	3 (0.1)	0	3 (0.1)
	Total	165 (3.3)	125 (2.5)	290 (5.9)	172 (3.5)	120 (2.4)	292 (5.9)

N: Number of subjects
Clinical pharmacology trials included: nn1436-4226, nn1436-4422, nn1436-4314, nn1436-4225, nn1436-4462, nn1436-4570, nn1436-4572, nn1436-4571, nn1436-4569
Exploratory/confirmatory trials included: nn1436-4383, nn1436-4466, nn1436-4465, NN1436-4480, NN1436-4479, NN1436-4625, NN1436-4477, NN1436-4481, NN1436-4478
Comparator: IGlar, IDeg, OD analogues

Abbreviations: Ico = insulin icodec, IDeg = insulin degludec; IGlar = insulin glargine; OD = once daily.

Product	Age range	Ico N (%)			Comparator N (%)		
		Male	Female	Total	Male	Female	Total
T2DM	18<= to <65 years	879 (17.8)	593 (12.0)	1472 (29.8)	778 (15.7)	596 (12.1)	1374 (27.8)
	65<= to <75 years	392 (7.9)	299 (6.0)	691 (14.0)	353 (7.1)	294 (5.9)	647 (13.1)
	Elderly (75<= years)	63 (1.3)	37 (0.7)	100 (2.0)	45 (0.9)	35 (0.7)	80 (1.6)
	Total	1334 (27.0)	929 (18.8)	2263 (45.8)	1176 (23.8)	925 (18.7)	2101 (42.5)
All subjects	18<= to <65 years	1025 (20.7)	714 (14.4)	1739 (35.2)	938 (19.0)	707 (14.3)	1645 (33.3)
	65<= to <75 years	409 (8.3)	302 (6.1)	711 (14.4)	362 (7.3)	303 (6.1)	665 (13.4)
	Elderly (75<= years)	65 (1.3)	38 (0.8)	103 (2.1)	48 (1.0)	35 (0.7)	83 (1.7)
	Total	1499 (30.3)	1054 (21.3)	2553 (51.6)	1348 (27.3)	1045 (21.1)	2393 (48.4)
All trials							
Hepatic Impairment	18<= to <65 years	10 (0.2)	10 (0.2)	20 (0.4)	0	0	0
	65<= to <75 years	2 (0.0)	3 (0.1)	5 (0.1)	0	0	0
	Total	12 (0.2)	13 (0.2)	25 (0.5)	0	0	0
Renal Impairment	18<= to <65 years	32 (0.6)	16 (0.3)	48 (0.9)	0	0	0
	65<= to <75 years	7 (0.1)	3 (0.1)	10 (0.2)	0	0	0
	Total	39 (0.7)	19 (0.4)	58 (1.1)	0	0	0
T1DM	18<= to <65 years	179 (3.4)	133 (2.5)	312 (5.9)	197 (3.7)	119 (2.2)	316 (6.0)
	65<= to <75 years	17 (0.3)	3 (0.1)	20 (0.4)	9 (0.2)	9 (0.2)	18 (0.3)
	Elderly (75<= years)	2 (0.0)	1 (0.0)	3 (0.1)	3 (0.1)	0	3 (0.1)
	Total	198 (3.7)	137 (2.6)	335 (6.3)	209 (3.9)	128 (2.4)	337 (6.4)
T2DM	18<= to <65 years	973 (18.3)	624 (11.8)	1597 (30.1)	797 (15.0)	604 (11.4)	1401 (26.4)
	65<= to <75 years	416 (7.8)	304 (5.7)	720 (13.6)	359 (6.8)	295 (5.6)	654 (12.3)
	Elderly (75<= years)	63 (1.2)	37 (0.7)	100 (1.9)	45 (0.8)	35 (0.7)	80 (1.5)
	Total	1452 (27.4)	965 (18.2)	2417 (45.5)	1201 (22.6)	934 (17.6)	2135 (40.2)

N: Number of subjects
Clinical pharmacology trials included: nn1436-4226, nn1436-4422, nn1436-4314, nn1436-4225, nn1436-4462, nn1436-4570, nn1436-4572, nn1436-4571, nn1436-4569
Exploratory/confirmatory trials included: nn1436-4383, nn1436-4466, nn1436-4465, NN1436-4480, NN1436-4479, NN1436-4625, NN1436-4477, NN1436-4481, NN1436-4478
Comparator: IGlar, IDeg, OD analogues

Abbreviations: Ico = insulin icodec, IDeg = insulin degludec; IGlar = insulin glargine; OD = once daily.

Product	Age range	Ico N (%)			Comparator N (%)		
		Male	Female	Total	Male	Female	Total
All subjects	18<= to <65 years	1194 (22.5)	783 (14.8)	1977 (37.3)	994 (18.7)	723 (13.6)	1717 (32.4)
	65<= to <75 years	442 (8.3)	313 (5.9)	755 (14.2)	368 (6.9)	304 (5.7)	672 (12.7)
	Elderly (75<= years)	65 (1.2)	38 (0.7)	103 (1.9)	48 (0.9)	35 (0.7)	83 (1.6)
	Total	1701 (32.1)	1134 (21.4)	2835 (53.4)	1410 (26.6)	1062 (20.0)	2472 (46.6)

N: Number of subjects
Clinical pharmacology trials included: nn1436-4226, nn1436-4422, nn1436-4314, nn1436-4225, nn1436-4462, nn1436-4570, nn1436-4572, nn1436-4571, nn1436-4569
Exploratory/confirmatory trials included: nn1436-4383, nn1436-4466, nn1436-4465, NN1436-4480, NN1436-4479, NN1436-4625, NN1436-4477, NN1436-4481, NN1436-4478
Comparator: IGlar, IDeg, OD analogues

Abbreviations: Ico = insulin icodec, IDeg = insulin degludec; IGlar = insulin glargine; OD = once daily.

Table 2-8 Total exposure by ethnic or racial origin

Product	Racial group	Ico N (%)	Comparator N (%)	Total N (%)
Clinical Pharmacology trials				
Hepatic Impairment	White	25 (100.0)	0	25 (100.0)
	Total	25 (100.0)	0	25 (100.0)
Renal Impairment	White	58 (100.0)	0	58 (100.0)
	Total	58 (100.0)	0	58 (100.0)
T1DM	Asian	12 (26.7)	12 (26.7)	24 (26.7)
	White	33 (73.3)	33 (73.3)	66 (73.3)
	Total	45 (100.0)	45 (100.0)	90 (100.0)
T2DM	Asian	25 (16.2)	1 (2.9)	26 (13.8)
	Other	1 (0.6)	1 (2.9)	2 (1.1)
	White	128 (83.1)	32 (94.1)	160 (85.1)
	Total	154 (100.0)	34 (100.0)	188 (100.0)
All subjects	Asian	37 (13.1)	13 (16.5)	50 (13.9)
	Other	1 (0.4)	1 (1.3)	2 (0.6)
	White	244 (86.5)	65 (82.3)	309 (85.6)
	Total	282 (100.0)	79 (100.0)	361 (100.0)
Exploratory/confirmatory clinical trials				
T1DM	Asian	51 (17.6)	72 (24.7)	123 (21.1)
	Black	9 (3.1)	2 (0.7)	11 (1.9)
	White	230 (79.3)	218 (74.7)	448 (77.0)
	Total	290 (100.0)	292 (100.0)	582 (100.0)
T2DM	American Indian	6 (0.3)	4 (0.2)	10 (0.2)

SYE: Subject years of exposure
Clinical pharmacology trials included: nn1436-4226, nn1436-4422, nn1436-4314, nn1436-4225, nn1436-4462, nn1436-4570, nn1436-4572, nn1436-4571, nn1436-4569
Exploratory/confirmatory trials included: nn1436-4383, nn1436-4466, nn1436-4465, NN1436-4480, NN1436-4479, NN1436-4625, NN1436-4477, NN1436-4481, NN1436-4478 Comparator: IGlar, IDeg, OD analogues

Full names for racial groups: American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander

Abbreviations: Ico = insulin icodec, IDeg = insulin degludec; IGlar = insulin glargine; OD = once daily.

Product	Racial group	Ico N (%)	Comparator N (%)	Total N (%)
T2DM	Asian	441 (19.5)	459 (21.8)	900 (20.6)
	Black	80 (3.5)	80 (3.8)	160 (3.7)
	Native Hawaiian	6 (0.3)	2 (0.1)	8 (0.2)
	Other	37 (1.6)	31 (1.5)	68 (1.6)
	Not Reported	15 (0.7)	17 (0.8)	32 (0.7)
	White	1678 (74.1)	1508 (71.8)	3186 (73.0)
	Total	2263 (100.0)	2101 (100.0)	4364 (100.0)
All subjects	American Indian	6 (0.2)	4 (0.2)	10 (0.2)
	Asian	492 (19.3)	531 (22.2)	1023 (20.7)
	Black	89 (3.5)	82 (3.4)	171 (3.5)
	Native Hawaiian	6 (0.2)	2 (0.1)	8 (0.2)
	Other	37 (1.4)	31 (1.3)	68 (1.4)
	Not Reported	15 (0.6)	17 (0.7)	32 (0.6)
	White	1908 (74.7)	1726 (72.1)	3634 (73.5)
	Total	2553 (100.0)	2393 (100.0)	4946 (100.0)
All trials				
	American Indian	6 (0.2)	4 (0.2)	10 (0.2)
	Asian	529 (18.7)	544 (22.0)	1073 (20.2)
	Black	89 (3.1)	82 (3.3)	171 (3.2)
	Native Hawaiian	6 (0.2)	2 (0.1)	8 (0.2)
	Other	38 (1.3)	32 (1.3)	70 (1.3)
	Not Reported	15 (0.5)	17 (0.7)	32 (0.6)
	White	2152 (75.9)	1791 (72.5)	3943 (74.3)
	Total	2835 (100.0)	2472 (100.0)	5307 (100.0)

SYE: Subject years of exposure
Clinical pharmacology trials included: nn1436-4226, nn1436-4422, nn1436-4314, nn1436-4225, nn1436-4462, nn1436-4570, nn1436-4572, nn1436-4571, nn1436-4569
Exploratory/confirmatory trials included: nn1436-4383, nn1436-4466, nn1436-4465, NN1436-4480, NN1436-4479, NN1436-4625, NN1436-4477, NN1436-4481, NN1436-4478
Comparator: IGlar, IDeg, OD analogues

Full names for racial groups: American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander.

Abbreviations: Ico = insulin icodec, IDeg = insulin degludec; IGlar = insulin glargine; OD = once daily.

2.4 Module SIV: Populations not studied in clinical trials

2.4.1 Exclusion criteria in pivotal clinical trials within the development programme

Table 2-9 Exclusion criteria in pivotal clinical studies within the development programme

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.	Known or suspected hypersensitivity to insulin analogues and excipients is not common. If a subject with known or suspected hypersensitivity is exposed to one of these, a severe immunological response with a life-threatening condition could occur.	No Contraindications (SmPC Section 4.3, Section 2 of the PL). Hypersensitivity to insulin icodec or to any of the excipients is listed as a contraindication in the product information for insulin icodec. Hypersensitivity will also be added to the list of ADRs reported in clinical trials in the EU-PI Hypersensitivity is an important identified risk for insulin icodec for the purposes of routine pharmacovigilance and aggregate reporting. It is not considered an important risk in the RMP, as it is well managed with routine risk minimisation measures and no additional pharmacovigilance activities or risk minimisation measure are planned or deemed necessary. It is not considered missing information.
Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods.	Pregnant and breast-feeding women are considered to be a vulnerable group. This was a standard exclusion criterion.	Yes Pregnancy and breast-feeding is included as missing information in the RMP as the safety profile of insulin icodec has not been established in pregnant or lactating patients with diabetes mellitus. In section 4.6 of the SmPC and Section 2 of the PL, the lack of clinical experience with insulin icodec during pregnancy or breast feeding is indicated: *Pregnancy* Because of the lack of experience during pregnancy, women of childbearing potential should be advised to discontinue

Criteria	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
		insulin icodec, if they wish to become pregnant. *Breast-feeding* There is no clinical experience with use of insulin icodec during breast-feeding and no information about excretion of insulin icodec in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from insulin icodec therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Cancer and medical history of cancer 5 years prior to trial entry (except basal cell skin cancer or squamous cell skin cancer).	Study subjects with cancer or recent history of cancer are usually receiving specialised treatment, with close monitoring. These subjects were excluded in all phase 3a studies, with the exception of NN1436-4481, as the population is considered vulnerable and in order not to jeopardise their safety and confound results of trials.	No There is no identified pharmacological mechanism of insulin icodec to suspect a higher carcinogenic potential compared to other insulins. Nonclinical studies investigating the effect of insulin icodec did not raise any concerns regarding carcinogenicity, genotoxicity, or mitogenicity. Clinical data did not show any increased frequency of neoplasms or tumours.

Abbreviations: ADR = adverse drug reaction; EU-PI = European Union product information; PL = product leaflet; SmPC = Summary of Product Characteristics

2.4.2 Limitations of ADR detection common to clinical trial 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 trial development programmes

Table 2-10 provides an overview of exposure in special populations from completed clinical pharmacology trials.

Table 2-10 Exposure by indication in special populations

Product	Population/ Indication	Special population	N	SYE
Clinical Pharmacology trials				
	Hepatic Impairment	Hepatic Impairment		
		Mild	6	NA
		Moderate	6	NA
		Severe	7	NA
	Renal Impairment	Renal Impairment		
		ESRD	10	NA
		Mild	12	NA
		Moderate	12	NA
		Severe	12	NA

N:Number of subjects, SYE: Subject years of exposure
Clinical pharmacology trials included: nn1436-4226, nn1436-4422, nn1436-4314, nn1436-4225, nn1436-4462, nn1436-4570, nn1436-4572, nn1436-4571, nn1436-4569
Exploratory/confirmatory trials included: nn1436-4383, nn1436-4466, nn1436-4465, NN1436-4480, NN1436-4479, NN1436-4625, NN1436-4477, NN1436-4481, NN1436-4478
Comparator: IGlar, IDeg, OD analogues

Mild Hepatic Impairment = Child-Pugh Grade A; Moderate Hepatic Impairment = Child-Pugh Grade B, Severe Hepatic Impairment = Child-Pugh Grade C.
Mild Renal Impairment = glomerular filtration rate of 60 - < 90 mL/min; Moderate Renal Impairment = glomerular filtration rate of 30 < 60 mL/min; Severe Renal Impairment = glomerular filtration rate of < 30 mL/min not requiring dialysis; End-stage Renal Disease (ERSD) = requiring haemodialysis treatment

An overview of special populations typically under-represented in clinical development programmes is presented in Table 2-11, with information and/or exposure to insulin icodec in the phase 3a, as of the DLP of the RMP.

Table 2-11 Exposure of special populations included or not in clinical trial development programme

Type of special population	Exposure and safety concerns
Pregnant and breast-feeding women	Pregnant and breast-feeding women, were not included in the randomised clinical trials investigating insulin icodec safety and efficacy. The experience with use of insulin icodec in female patients is limited. A total of 3 subjects receiving insulin icodec in the phase 3a programme became pregnant during the study. All three were in their first trimester and either discontinued treatment with the study drug upon diagnosis or were diagnosed as pregnant at the end of their participation in the study. Pregnancy and breast-feeding has been included as missing information in the RMP to monitor for adverse effects in this population in the post-marketing setting (see further details in Section 2.7.3.3).
Patients with hepatic impairment	The pharmacokinetic characteristics of insulin icodec in subjects with hepatic impairment were evaluated in one study (NN1436-4570) with 25 subjects enrolled. (see Table 2-10). No pharmacokinetic differences of clinical relevance or safety concerns were identified in this study. For all the phase 3a studies, with the exception of ONWARDS 5 (NN1436-4481), hepatic impairment was an exclusion criterion. A total of 15 subjects (7 to insulin icodec, 8 to comparator) were exposed to study drug during the phase 3 programme with hepatic impairment. Impaired hepatic function was defined as having a total score of >2 according to a modified Child-Pugh classification based on low serum albumin and/or increased bilirubin Overall, the AE profile for insulin icodec appears similar to daily basal insulin in subjects with hepatic impairment and no clinically relevant interactions between insulin icodec and any intrinsic factor were found based on the insulin icodec development programme. Use in patients with hepatic impairment has not been included as missing information in the RMP as there is no medical or scientific reason to expect a different safety profile of insulin icodec in this population, considering the mechanism of action and elimination of insulin icodec. Hepatic function will be monitored through routine pharmacovigilance activities in clinical trials and in the post-marketing setting. It is acknowledged in Section 4.8 of the SmPC that "*safety data in patients with hepatic impairment is limited*".

Type of special population	Exposure and safety concerns
Patients with renal impairment	The pharmacokinetic characteristics of insulin icodec in subjects with renal impairment were evaluated in one study (NN1436-4226) with 58 subjects enrolled. (see Table 2-10). Total exposure to insulin icodec was higher in subjects with impaired renal function and no safety concerns were identified from this study. For all the phase 3a studies, with the exception of ONWARDS 5 (NN1436-4481), severe renal impairment was an exclusion criterion. In the insulin icodec treatment arm of the phase 3a programme, 38.6% (837) of the 2170 subjects had mild renal impairment (eGFR of ≥60 and <90 mL/min/1.73 m^2), 9.2% (207) had moderate renal impairment (eGFR of ≥30 and <60 mL/min/1.73 m^2), and 0.2 % (5) had severe renal impairment (eGFR of <30 mL/min/1.73 m^2 without dialysis). No pronounced treatment difference in AEs by SOC, and by SOC and PT were observed across baseline renal function groups that differ markedly from the general pattern observed. Use in patients with renal impairment has not been included as missing information in the RMP as there is no medical or scientific reason to expect a different safety profile of insulin icodec in this population, considering the number of subjects enrolled with renal impairment, as well as the mechanism of action, and elimination of insulin icodec. Renal function will be monitored through routine pharmacovigilance activities in clinical trials and in the post-marketing setting. .
Patients with cardiac impairment	No clinical pharmacology studies were conducted evaluating the pharmacokinetic or pharmacodynamic properties of insulin icodec in patients with identified cardiovascular disease. For all phase 3a trials, except ONWARDS 5 (NN1436-4481), subjects were to be excluded if they had certain pre-existing CV disorders. At screening, of the 2170 enrolled in phase 3a studies, 70.3% from the insulin icodec treatment arm had vascular disorder and 20.9% had cardiac disorders. There was no indication of an increased risk of CV disorders in the insulin icodec group compared to the daily basal insulin group based on the evaluation of EAC-confirmed CV events, ECG data and meta-analysis of MACE from the insulin icodec phase 3a trials. The numbers of EAC-confirmed CV events were low and were reported in similar proportions of subjects in the insulin icodec group and daily basal insulin group in the phase 3a pool, and there were no clinically relevant differences between insulin icodec and daily basal insulin in the improvement or deterioration of ECG categories. Subjects treated with insulin icodec had a similar incidence of and time to first EAC confirmed MACE when compared to those treated with a daily basal insulin analogue. Therefore, this population has not been included as missing information in the RMP.

Type of special population	Exposure and safety concerns
Patients aged 75 years of age and over	In the insulin icodec treatment arm, a total of 103 subjects aged 75 years or older were enrolled as part of the phase 3a programme. Of these subjects, 100 were diagnosed with T2D and 3 were diagnosed with T1D. In subjects age ≥75 years enrolled in phase 3a studies, the proportions of subjects reporting AEs were higher in the insulin icodec group with mainly a higher reporting of non-serious events. The number of severe AEs were reported by similar proportions of subjects age ≥75 years in both treatment groups. Use in patients aged 75 years or older has not been included as missing information in the RMP as there is no medical or scientific reason to expect a different safety profile of insulin icodec in this population. According to ICH E7, a minimum of 100 patients would usually allow detection of clinically important differences. Refer to Section 4.2 and 4.8 of the SmPC.

Abbreviations: AE = adverse event; CV = cardiovascular; EAC =event adjudication committee; ECG = electrocardiogram; GFR = glomerular filtration rate; MACE = major adverse cardiovascular event; PT = preferred term; RMP = risk management plan; SOC = system organ class.

2.4.3.1 Baseline characteristics of the phase 3a programme

In Clinical Summary 2.74 Section 1.2.4.2, the baseline characteristics of the phase 3a clinical trial programme are described. Characteristics evaluated within this population include body weight, smoker status, kidney function, liver function, concomitant illnesses, and concomitant medications. Overall, across the clinical development programme, sufficient numbers of subjects were enrolled, to enable adequate characterisation of the safety profile of insulin icodec across a broad range of subjects.

2.5 Module SV: Post-authorisation experience

2.5.1 Post-authorisation exposure

This section is not applicable, as this RMP for insulin icodec is submitted with the application for marketing authorisation. Hence, no patients have been exposed to insulin icodec in the post-marketing setting.

2.5.1.1 Method used to calculate exposure

Not applicable, as no patients have been exposed to insulin icodec in the post-marketing setting.

2.5.1.2 Exposure

Not applicable, as no patients have been exposed to insulin icodec in the post-marketing setting.

2.5.2 Post-authorisation use and off-label use

Not applicable, as no patients have been exposed to insulin icodec in the post-marketing setting.

2.6 Module SVI: Additional EU requirements for the safety specification

2.6.1 Potential for misuse for illegal purposes

There is potential for all insulin products to be misused either by patients with or without diabetes. Examples of misuse are intentional overdoses, suicide attempts and use for anabolic purposes by body builders or endurance athletes.[53-55]

No cases of misuse or abuse of insulin icodec were observed in the clinical development programme.

Reports of misuse for illegal purposes will be monitored through routine pharmacovigilance. From the data available, Novo Nordisk does not consider potential for misuse to be a safety concern for insulin icodec.

2.7 Module SVII: Identified and potential risks

2.7.1 Identification of safety concerns in the initial RMP submission

2.7.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks that are not considered important for the purpose of planning of risk management for insulin icodec are grouped based on the rationale for non-inclusion (see Table 2-12). Overall, the impact of these risks on the benefit–risk balance of insulin icodec is considered to be low. The risks are considered to be appropriately managed and mitigated in the proposed product information for insulin icodec.

The overall safety profile of insulin icodec in the initial RMP submission is based on data from the multiple dose phase 3a clinical trials (NN1436-4477, -4478, -4479, -4480. -4481, and -4625) for which study subject exposure is presented in Section 2.3.

Table 2-12 Risks not considered important for inclusion in the list of safety concerns

Risk	Benefit−risk impact
Risks with minimal clinical impact on patients in relation to the severity of the indication treated	
Injection site reactions	Injection site reactions are listed as a common ADR in the EU-PI as these reactions were reported in between 1-10% of patients treated with insulin icodec. No serious injection site reactions were reported across the phase 3a programme. The impact of the injection site reactions on the benefit-risk balance of insulin icodec is considered minimal based on the severity of the events (77 of 81 adverse events [95%] were mild). Injection site reactions are considered expected for any drug administered by subcutaneous injection such as insulin icodec. Additionally, given the once weekly injection regimen, the corresponding reduction in injection frequency, compared to daily injection regimens, is expected to further reduce the frequency of injection site reactions. This, combined with the transient nature of these adverse events, is consistent with minimal clinical consequence and is, therefore, considered a non-important risk.

Risk	Benefit−risk impact
Peripheral oedema	Peripheral oedema is listed as a common ADR in the EU-PI as these reactions were reported in between 1-10% of patients treated with insulin icodec. No serious events of peripheral oedema were reported across the phase 3a programme. The risk of peripheral oedema has minimal impact on the benefit-risk relationship due to the mild severity and non-seriousness of the AEs. This, combined with the transient nature of these adverse events, is consistent with minimal clinical consequence and is, therefore, considered a non-important risk.
Risks with potentially serious clinical consequences that may occur at low frequencies and therefore are considered to be acceptable in relation to the severity of the indication treated	
Hypersensitivity	Hypersensitivity is listed as an uncommon ADR in the EU-PI as these reactions were reported in between 0.1- 1% of patients treated with insulin icodec. As with other insulins, allergic reactions may occur with insulin icodec. Hypersensitivity reactions to protein drugs can range from being mild to severe life-threatening allergic or immune reactions. The impact of the risk of hypersensitivity reactions on the benefit-risk balance of insulin icodec is considered minimal based on the low frequency of allergic reactions. The risk is considered well-managed by the information shared to patients and healthcare professionals in the SmPC and PL and will be monitored through routine pharmacovigilance activities, including single case reporting, Periodic Benefit-Risk evaluation reports (PBRERs)/Periodic Safety Update Reports (PSURs) and signal detection. No additional pharmacovigilance or risk minimisation activities are planned or deemed necessary.
Known risks that require no further characterisation and the potential clinical consequences will be monitored via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers	
Immunological events – formation of neutralising antibodies	The risk of neutralising antibodies is mentioned under Warning and precautions of the EU-PI. The potential of insulin icodec neutralising antibody development does not impact the benefit-risk balance because the immunogenic response did not result in any safety issues, reduced efficacy, or an increase in insulin doses to maintain glycaemic control. Based on the available data, the risk for Immunological events – formation of neutralising antibodies is sufficiently characterised and therefore not considered as a safety concern in the RMP.
Hypoglycaemia, including prolonged hypoglycaemia	Hypoglycaemia is an important identified and well characterised risk associated with all insulins. The general risk for hypoglycaemia is not included in the RMP as a safety concern for other insulins and not considered relevant to include for insulin icodec. The risk of hypoglycaemia is considered to be adequately managed by the information in section 4.4 and 4.8 of the SmPC and will be monitored through routine pharmacovigilance activities, including single case reporting, Periodic Benefit-Risk evaluation reports (PBRERs)/Periodic Safety Update Reports (PSURs) and signal detection. For prolonged hypoglycaemia, the data based on continuous glucose monitoring (CGM) from ONWARDS 1, 2, 4 and 6, demonstrated no concern regarding prolonged hypoglycaemia during treatment with insulin icodec compared to daily basal insulin, with similar median durations of CGM-verified clinically significant (level 2) hypoglycaemic episodes for the two treatment groups. Therefore, ‘prolonged hypoglycaemia’ is not considered important for inclusion in the list of safety concerns. However, considering its potential impact, the risk of prolonged hypoglycaemia will be monitored and presented as a separate topic under the risk of ‘Hypolycaemia’ in future PSURs.

Risk	Benefit–risk impact
Other reasons for considering the risks not important	
Hepatic impairment	Hepatic impairment was not considered a safety concern in regard to initiation of insulin icodec therapy. Overall, the AE profile in subjects with hepatic impairment for insulin icodec appears similar to daily basal insulin and no clinically relevant interactions between insulin icodec and any intrinsic factor were found based on the insulin icodec development programme. Additionally, no pharmacokinetic differences of clinical relevance or safety concerns were observed in a phase 1 study evaluating the pharmacokinetic characteristics of insulin icodec in subjects with varying degrees of hepatic impairment. As the need to maintain glycaemic control is vital for patients with diabetes mellitus, the safety data does not indicate a difference between treatment arms with regards to adverse event reporting in subjects with T2D and hepatic impairment, the impact on the benefit risk profile is expected to be minimal.
Renal impairment	Renal impairment was not considered a safety concern in regard to initiation of insulin icodec therapy. In the phase 3a programme, no pronounced treatment difference in AEs by SOC, and by SOC and PT were observed across baseline renal function groups that differ markedly from the general pattern observed. In a phase 1 study (NN1436-4226), total exposure to insulin icodec was higher in subjects with impaired renal function, but no safety concerns were identified from this study. As the need to maintain glycaemic control is vital for patients with diabetes mellitus, the safety data does not indicate a difference between treatment arms with regards to adverse event reporting in subjects with T2D and renal impairment, the impact on the benefit risk profile is expected to be minimal.
Cardiovascular disease	There was no indication of an increased risk of CV disorders in the insulin icodec group compared to the daily basal insulin group based on the evaluation of EAC-confirmed CV events, ECG data and meta-analysis of MACE from the insulin icodec phase 3a trials. The numbers of EAC-confirmed CV events were low and were reported in similar proportions of subjects in the insulin icodec group and daily basal insulin group in the phase 3a pool, and there were no clinically relevant differences between insulin icodec and daily basal insulin in the improvement or deterioration of ECG categories. Subjects treated with insulin icodec had a similar incidence of and time to first EAC confirmed MACE when compared to those treated with a daily basal insulin analogue. As the need to maintain glycaemic control is vital for patients with diabetes mellitus, and the safety data does not indicate a difference between treatment arms with regards to adverse event reporting in subjects with diabetes mellitus and cardiovascular disease, the impact on the benefit risk profile is expected to be minimal.

Risk	Benefit–risk impact
Elderly	Use in patients aged 75 years or older has not been included as missing information in the RMP as there is no medical or scientific reason to expect a different safety profile of insulin icodec in this population. Routine surveillance of post-marketing data will be used to monitor for any potential changes to the safety profile. Elderly patients are included within the indication for insulin icodec and guidance for the usage of insulin icodec for elderly patients is included in the EU PI. According to ICH E7, a minimum of 100 patients would usually allow detection of clinically important differences. Refer to Section 4.1 and 4.8 of the SmPC. As the need to maintain glycaemic control is vital for patients with diabetes mellitus, and the safety data does not indicate a difference compared to the broader population, the impact on the benefit risk profile is expected to be minimal.

Abbreviations: ADR = adverse drug reaction ; AE = adverse event; EU-PI = European Union product information.

2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Risks considered important for inclusion in the list of safety concerns for further evaluation as part of the pharmacovigilance plan or risk minimisation activities and their benefit–risk impact are briefly discussed in Table 2-13. Further details on the safety concerns are presented in Section 2.7.3.

Table 2-13 Brief presentation of important safety concerns

Safety concerns	Benefit–risk impact
Important identified risks	
None	
Important potential Risks	
Medication errors due to mix-up	While medication error-related adverse events were reported as part of the phase 3a programme, the unrepresentative nature of clinical practice, and the appearance of the device (labelling and cartridge colour) relative to the expected post-authorisation experience limit the value of these data in terms of characterising this risk. It is anticipated that post-authorisation data will be of much greater value in this regard. Three events were reported with PTs of 'product dispensing error' (1) and 'wrong product administered' (2) in the insulin icodec arm in the phase 3a programme. These events are assessed to be unlikely related to insulin icodec exposure by the Investigator. Medication errors are a known risk for many insulin products and can result in loss of glycaemic control depending on the nature of the mix-up. Serious clinical consequences related to over- or under-dosing due to product mix-ups represent an important consideration for the benefit-risk assessment for the risk of product mix-up. Any impact of this risk on the benefit–risk balance of insulin icodec is anticipated to be reduced by the measures taken in the labelling and product appearance to mitigate this risk.
Medication errors during switch from daily basal insulin	In the insulin icodec treatment arm, a cluster of overdose and dosing error events (25 events) with the PTs (accidental overdose, prescribed overdose, overdose, incorrect dose administered, and extra dose administered) occurred during the first two injections in NN1436-4478, -4480 and -4625 where a one-time additional dose was given for the first dose. These types

Safety concerns	Benefit−risk impact
	of events are, however, evenly distributed throughout the duration of the study in the comparator group and no similar cluster is detected. The majority of these events (15/25) occurred at the second injection where the one-time additional dose was intended to be reduced. None of these events were serious or resulted in severe hypoglycaemia. Only level 1 and level 2 hypoglycaemic episodes related to insulin icodec exposure were reported. Medication errors are a known risk for many insulin products and can result in loss of glycaemic control, of varying degrees of severity, depending on the nature of dosing error. Serious clinical consequences related to dosing errors or overdoses due to medication errors represent an important consideration for the benefit-risk assessment for this risk. Any impact of this risk on the benefit–risk balance of insulin icodec is anticipated to be reduced by the measures taken in the product information to mitigate this risk.
Missing information	
Pregnancy and breast-feeding	The data available concerning insulin icodec use in pregnant or breast-feeding women is limited (3 subjects in the phase 3a programme exposed to insulin icodec; 1st trimester for all) and the exclusion criteria for all studies with insulin icodec as the investigative medicinal product includes women who are pregnant or breast-feeding. No congenital anomalies have been reported in children of women treated in the insulin icodec group. One pregnancy in the insulin icodec group had the outcome of PT abortion spontaneous, after the main-on-treatment period, and was reported as an SAE. Non-clinical studies have not revealed any fetotoxic or teratogenic potential for insulin icodec. There is no clinical experience with use of insulin icodec during breast-feeding. There is no information about excretion of insulin icodec in human milk. In rats, insulin icodec exposure after breast-feeding was low and absorption of insulin icodec from milk is not considered to pose any metabolic effects. However, a risk to the newborns/infants cannot be excluded. If evidence should emerge in the post-marketing setting that indicates a different safety profile of insulin icodec in this population, the impact on the benefit-risk balance will depend on the type and incidence rate of the adverse effects as well as on effectiveness of risk mitigating measures. Refer to EU-PI section 4.6 Fertility, pregnancy, and lactation.

Abbreviations: ADR = adverse drug reaction; EU-PI = European Union product information; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event.

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

This section is not applicable, as this is the first RMP submitted to obtain marketing authorisation for insulin icodec.

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

2.7.3.1 Important potential risk: Medication errors due to mix-up

Potential mechanisms

Mediation errors concerning product mix-ups can occur:

- When the product was prescribed by physician.
- When the product was dispensed, e.g. at pharmacy
- When the product was administered.
- As an error in the monitoring required to administer the product correctly (e.g. recommendations in the label were not followed).

Evidence source and strength of evidence:

Medication errors are a known risk for many insulin products. Medication errors in clinical trials are systematically collected and the cases are well documented. However, clinical trials are unrepresentative of clinical practice and the appearance of the device (labelling and cartridge colour) are not the same as the marketed device.

Characterisation of the risk:

Mix-ups between basal and bolus insulin may lead to hyper- or hypoglycaemia and the corresponding consequences of the lack of glycaemic control.

While medication error-related adverse events were reported as part of the phase 3a programme, the unrepresentative nature of clinical practice, and the appearance of the device (labelling and cartridge colour) relative to the expected post-authorisation experience limit the value of these data in terms of characterising this risk.

Usability testing to evaluate the frequency of common errors of product identification demonstrated no misidentification errors on the part of study subjects, health care providers and pharmacy staff.

Data from clinical trials:

All medication error related events from the phase 3a programme are presented in Table 2-14. The specific MedDRA PTs for medication error-related AEs are further presented in Table 2-15).

Table 2-14 Medication errors incl. misuse and abuse (predefined MedDRA search) - on-treatment/main-on-treatment - summary - safety analysis set - phase 3a pool

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2170				2170			
PYE (years)	1681.23				1680.58			
Events	37	(1.7)	40	3.34	31	(1.4)	36	2.77
Serious								
Yes	1	(0.0)	1	0.09	2	(0.1)	2	0.16
No	36	(1.7)	39	3.24	29	(1.3)	34	2.61
Missing	0				0			
Severity								
Severe	1	(0.0)	1	0.09	0			
Moderate	10	(0.5)	10	0.85	6	(0.3)	6	0.47
Mild	27	(1.2)	29	2.40	25	(1.2)	30	2.30
Missing	0				0			
Related to basal insulin								
Probable	18	(0.8)	19	1.60	4	(0.2)	5	0.40
Possible	4	(0.2)	4	0.30	0			
Unlikely	16	(0.7)	17	1.44	27	(1.2)	31	2.37
Missing	0				0			
Related to technical complaint for basal insulin								
Yes	1	(0.0)	1	0.08	1	(0.0)	1	0.08
No	36	(1.7)	39	3.26	30	(1.4)	35	2.69
NA	0				0			
Missing	0				0			

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, NA: Not applicable, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the end-date of the on-treatment period or the last planned visit in the main part of the trial. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6. MedDRA version 24.1. Events found via MedDRA queries.

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Outcome								
Fatal	0				0			
Not recovered/not resolved	0				1	(0.0)	1	0.04
Recovered/resolved with sequelae	0				0			
Recovering/resolving	0				0			
Recovered/resolved	37	(1.7)	40	3.34	30	(1.4)	35	2.73
Unknown	0				0			
Missing	0				0			

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, NA: Not applicable, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the end-date of the on-treatment period or the last planned visit in the main part of the trial. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6. MedDRA version 24.1. Events found via MedDRA queries.

Table 2-15 Medication errors incl. misuse and abuse (predefined MedDRA search) - adverse events by system organ class and preferred term - on-treatment/main-on-treatment - summary - safety analysis set - phase 3a pool

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2170				2170			
PYE (years)	1681.23				1680.58			
Events	37	(1.7)	40	3.34	31	(1.4)	36	2.77
Injury, poisoning and procedural complications	36	(1.7)	39	3.26	30	(1.4)	35	2.73
Accidental overdose	14	(0.6)	15	1.24	4	(0.2)	5	0.41
Incorrect dose administered	6	(0.3)	6	0.52	5	(0.2)	7	0.52
Prescribed overdose	5	(0.2)	5	0.47	0			
Overdose	4	(0.2)	4	0.28	3	(0.1)	3	0.21
Medication error	2	(0.1)	2	0.16	3	(0.1)	3	0.25
Product administration error	1	(0.0)	1	0.09	2	(0.1)	2	0.12
Product dispensing error	1	(0.0)	1	0.09	0			
Underdose	1	(0.0)	1	0.08	5	(0.2)	5	0.36
Accidental underdose	1	(0.0)	1	0.08	0			
Extra dose administered	1	(0.0)	1	0.08	1	(0.0)	1	0.08
Wrong product administered	1	(0.0)	2	0.16	6	(0.3)	6	0.53
Wrong dose	0				2	(0.1)	2	0.16
Intentional overdose	0				1	(0.0)	1	0.08
Psychiatric disorders	1	(0.0)	1	0.08	1	(0.0)	1	0.04
Drug abuse	1	(0.0)	1	0.08	0			
Drug dependence	0				1	(0.0)	1	0.04

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the end-date of the on-treatment period or the last planned visit in the main part of the trial. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6. MedDRA version 24.1. Events found via MedDRA queries

Notably, non-serious AEs with the PTs Product dispensing error (1 AE) and Wrong product administered (2 AEs) were reported in the insulin icodec arm in the phase 3a programme. These events are assessed to be unlikely related to insulin icodec exposure by the Investigator.

Risk factors and risk groups

Patients with diabetes treated with basal–bolus insulin therapy (or other injectable medicine), patients with diabetes living with another person with diabetes, and visually impaired or colour-blind patients may be at a higher risk.

Preventability

Information provided to patients, and caregivers, with the medication and the product differentiation strategy are expected to limit the frequency of these kinds of medication errors.

Impact on the benefit-risk balance of the product

While clinical consequences resulting from a dosing error related to product mix-up can be serious, the impact on the benefit–risk balance of insulin icodec is anticipated to be low to moderate based on the measures taken in the product information, patient/carer's educational guide and product differentiation strategy to mitigate this risk and the clinical consequence to these medication errors.

Public health impact

The public health impact is anticipated to be sufficiently minimised through the product information and the product differentiation strategy. Usability testing conducted in the EU (UT-257) revealed health care professionals, pharmacy staff, and patients could correctly distinguish insulin icodec from other basal and bolus insulins, as well as pen-injectable therapies (including GLP-1 receptor agonists) with no documented misidentification errors.

2.7.3.2 Important potential risk: Medication errors during switch from daily basal insulin

Potential mechanisms

The mechanism intrinsic to insulin icodec's long half-life, requires consideration when switching from daily basal insulin products to insulin icodec. For the first injection only, a one-time additional dose is recommended to be utilised to quickly bring plasma concentrations up to efficacious levels so as to minimise the risk of hyperglycaemia, due to inadequate plasma insulin levels, during the switch to insulin icodec. After the first dose is administered, the following dose is lowered to a level appropriate to achieve glycaemic control and predicated on the daily basal insulin dosing regimen used prior to initiation with insulin icodec. All subsequent dosing is based on individual needs, while considering the balance between glycaemic control and the risk of hypoglycaemia. To ensure that patients switching to therapy with insulin icodec do so in a safe way with correct dosing, the SmPC contains a dose calculation table describing the appropriate one-time additional and following dose to be administered according to the prior daily basal insulin regimen.

Incorrect dosing of the one-time additional dose, or following doses, can potentially result in hypoglycaemic events due to overdosing or hyperglycaemic events in the case of underdosing.

Potential medication errors leading to these dosing concerns can occur

- When the product was prescribed by physician.
- When the product was dispensed, e.g. at pharmacy
- When the product was administered.
- An error in the monitoring required to administer the product correctly (e.g. recommendations in the label were not followed).

Evidence source and strength of evidence:

Medication errors are a known risk for many insulin products. Medication errors in clinical trials are systematically collected and the cases are well documented. However, clinical trials are unrepresentative of clinical practice.

Completed therapeutic confirmatory trials using a device in which insulin icodec was used as the investigational drug are the evidence sources of this risk.

Characterisation of the risk:

Insulin icodec is a novel once-weekly insulin and has a recommended dosing strategy for switching to insulin icodec from daily basal insulins. This strategy is not applicable to insulin naïve patients. Adverse event data from the phase 3a programme confirmed that medication errors related to overdoses and dosing errors occurred during the first two injections of insulin icodec.

Data from clinical trials:

Non-serious adverse events were reported concerning medication errors with potential dosing concerns following insulin icodec exposure (see Table 2-16). A cluster of overdose and dosing error events (25 events) were reported with the PTs accidental overdose, prescribed overdose, overdose, incorrect dose administered, and extra dose administered. These events occurred during the first two injections of insulin icodec in NN1436-4478, -4480, and -4625 where a one-time additional dose was given as part of the switch from a daily basal insulin to insulin icodec, as specified by the respective protocols. In comparison, these types of events are more broadly distributed across the duration of the studies in the comparator group and no similar cluster is detected in that treatment arm. The overall frequency of these AEs was comparable between treatment arms (see Table 2-16), and it is the clustering of AEs during the first two injections of insulin icodec that is of interest. The AEs were all reported with mild or moderate severity and with outcomes of 'recovered'. Clinical consequences in the form of co-reported level 1 and level 2 hypoglycaemic episodes were reported, yet no related level 3/severe hypoglycaemic episodes were reported.

Table 2-16 Medication errors related to mis-dosing - on-treatment/main-on-treatment - summary - safety analysis set - phase 3a pool

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2170				2170			
PYE (years)	1681.23				1680.58			
Events	30	(1.4)	31	2.59	13	(0.6)	16	1.22
Serious								
Yes	0				2	(0.1)	2	0.16
No	30	(1.4)	31	2.59	11	(0.5)	14	1.06
Missing	0				0			
Severity								
Severe	0				0			
Moderate	9	(0.4)	9	0.77	3	(0.1)	3	0.24
Mild	21	(1.0)	22	1.83	10	(0.5)	13	0.98
Missing	0				0			
Related to basal insulin								
Probable	15	(0.7)	16	1.35	2	(0.1)	3	0.24
Possible	4	(0.2)	4	0.30	0			
Unlikely	11	(0.5)	11	0.95	11	(0.5)	13	0.98
Missing	0				0			
Related to technical complaint for basal insulin								
Yes	1	(0.0)	1	0.08	1	(0.0)	1	0.08
No	29	(1.3)	30	2.51	12	(0.6)	15	1.14
NA	0				0			
Missing	0				0			

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, NA: Not applicable, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the end-date of the on-treatment period or the last planned visit in the main part of the trial. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6. MedDRA version 24.1. Events found via MedDRA queries.

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Outcome								
Fatal	0				0			
Not recovered/not resolved	0				0			
Recovered/resolved with sequelae	0				0			
Recovering/resolving	0				0			
Recovered/resolved	30	(1.4)	31	2.59	13	(0.6)	16	1.22
Unknown	0				0			
Missing	0				0			

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, NA: Not applicable, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the end-date of the on-treatment period or the last planned visit in the main part of the trial. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6. MedDRA version 24.1. Events found via MedDRA querie

Risk factors and risk groups

Patients with diabetes switching from daily basal insulins to insulin icodec represent the most significant risk group.

Preventability

The instructions included in the EU-PI are expected to limit the frequency of these kinds of medication errors. The information in the product information has been optimised compared to the information in the study protocols in anticipation of insulin icodec usage in a post-marketing setting. Briefly, the information is provided to assist patients in safely switching to insulin icodec in the following section of the EU-PI:

- In "Switch from once- or twice-daily basal insulin medicinal products to Awiqli in type 2 and type 1 diabetes" in Section 4.2 of the SmPC (Posology) – this includes a dose calculation table with recommended one-time additional doses and subsequent doses based on the prior daily basal dosing regimen.
- In "Switch between other insulins and Awiqli" in Section 4.4 of the SmPC (Special warnings and precautions for use) encouraging consultation with a physician before or during switching.
- In Section 4.9 of the SmPC (Overdose), including specific warning concerning the risk for overdose if the one-time additional dose continues to be taken with subsequent dosing.
- In Section 2 of the PL (What you need to know before using Awiqli), there is specific recommendation regarding consultation with a physician, and actively discouraging the use of the increased first dose for subsequent doses.
- In Section 3 of the PL (How to use Awiqli), switching to insulin icodec is discussed with specific mention that a doctor should prescribe you the first and second dose, and that subsequent doses should be determined in consultation with a doctor.

Similarly, in Section 4.4 of the SmPC (Special warnings and precautions for use), the section concerning the avoidance of medication errors stipulates that "Patients who are blind or have poor vision must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device".

Furthermore, the implementation of an additional risk minimisation measure in the form of a patient/carer's educational guide includes necessary instructions to minimise the risk of medication errors during switch from daily basal insulin.

Impact on the benefit-risk balance of the product

While medication errors in clinical trials are not necessarily predictive of what the post-marketing experience will be, confirmation of these dosing errors during these studies indicates a potential for related errors in a post-marketing setting. Further, while the clinical consequences to a large dosing error could be significant, the impact on the benefit–risk balance of insulin icodec is anticipated to be lessened based on the measures taken in the product information as well as patient/carer's educational guide to mitigate this risk and when considering the need for indicated patients with diabetes mellitus to controlling their blood glucose and absence of other therapies.

Public health impact

The public health impact is anticipated to be sufficiently minimised through the EU-PI and product label.

2.7.3.3 Missing information – Pregnancy and breast-feeding

Evidence source

No signs of maternal toxicity and no effects on fertility, embryo-foetal survival, pre- or post-implantation loss, placental weight, foetal weight or sex ratio were observed as result of insulin icodec exposure.

No evidence exists at present indicating if insulin icodec can switch to breast milk following maternal exposure.

The experience with insulin icodec exposure of pregnant and/or breast-feeding patients in the insulin icodec clinical development programme is very limited. A total of 3 subjects receiving insulin icodec in the phase 3a programme became pregnant during the study. All three were in their first trimester and either discontinued treatment with the study drug upon diagnosis or were diagnosed as pregnant at the end of their participation in the study. Females who are pregnant, breast-feeding, intend to become pregnant, or are of childbearing potential and are not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice) were to be excluded from the ONWARDS program.

Population in need of further characterisation

The safety profile of insulin icodec has not been established in pregnant or lactating patients with diabetes mellitus.

The product information provides the information that there are no data available on the use of insulin icodec in pregnant or breast-feeding women and provides further guidance for patients who wish to become pregnant and during breastfeeding. Use in pregnancy and lactation will be continuously monitored by routine pharmacovigilance activities in the post-marketing setting.

2.8 Module SVIII: Summary of safety concerns

Table 2-17 Summary of safety concerns - insulin icodec/diabetes mellitus

Summary of safety concerns	
Important identified risks	None
Important potential risks	Medication errors due to mix-up Medication errors during switch from daily basal insulin
Missing information	Pregnancy and breast-feeding

3 Pharmacovigilance plan

3.1 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

3.1.1 Specific adverse reaction follow-up questionnaires

Novo Nordisk aims to minimise the variable quality of the spontaneously reported medically-confirmed medication errors. Where information is limited or ambiguous, follow-up attempts with a healthcare professional will be made to ascertain the missing information. There is a series of questions for use in retrieving information required to maximise the evaluation of the data across all of Novo Nordisk's insulins. The list of questions is attached in Annex 4A and is expected to develop over time in response to feedback from health authorities and health care professionals. Data retrieved using the follow-up questionnaires will help Novo Nordisk in better characterising the risks to patients for "Medication errors due to mix-up" and "Medication errors during switch from daily basal insulin".

3.1.2 Other forms of routine pharmacovigilance activities

No other forms of routine pharmacovigilance activities are proposed.

3.2 Additional pharmacovigilance activities

There are currently no ongoing or planned additional pharmacovigilance activities for insulin icodec.

4 Plans for post-authorisation efficacy studies

There are currently no plans for post-authorisation efficacy studies for insulin icodec nor have any post-authorisation efficacy studies been imposed.

5 Risk minimisation measures

5.1 Routine risk minimisation measures

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important identified risks	
None	
Important potential risks	
Medication errors due to mix-up	***Routine risk communication:*** • The risk of mix-ups is presented in Section 4.4 of the SmPC and Section 2 of the PL. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • Instructions for avoidance of medication errors are described in Section 4.4 of the SmPC and Section 2 of the PL • Recommendations in Section 4.4 of the SmPC and Section 3 of the PL indicates that patients with impaired vision require assistance from a person with good vision

Safety concern	Routine risk minimisation measures
	• Product appearance is described in Section 6 of the PL to prevent misidentification of medicine ***Other risk minimisation measures beyond the Product Information:*** • Product differentiation strategy to reduce misidentification; includes trade name, label text, colour branding of the carton, container label and cartridge holder. • This medicine will only be available by prescription.
Medication errors during switch from daily basal insulin	***Routine risk communication:*** • The risk related to switching from daily basal insulin products is presented in Sections 4.2, 4.4, and 4.9 of the SmPC and Section 2 of the PL ***Routine risk minimisation activities recommending specific clinical measures to address the risk****:* • Instructions for switching from other daily basal insulins to insulin icodec, including a dose calculation table presenting the recommended one-time additional dose and second dose based on the daily basal insulin dosing regimen, are presented in Section 4.2 of the SmPC • Patients must be instructed to check that they inject the correct dose, especially in the first and second injection (Section 4.4 of the SmPC). It is also indicated in Section 4.2 of the SmPC and Section 2 of the PL that the one-time additional dose is not to be continued with subsequent doses • Patients who are uncertain about the correct dose must be instructed to consult their physician for further guidance (Section 4.4 of the SmPC) • A recommendation to only begin a switch to insulin icodec from another insulin under medical supervision is included in Section 4.4. of the SmPC and Section 2 of the PL • In Section 3 of the PL, switching to insulin icodec is discussed with specific mention that a doctor should prescribe you the first and second dose, and that subsequent doses should be determined in consultation with a doctor • In Section 4.9 of the SmPC, specific warning is included concerning the risk for overdose if the one-time additional dose continues to be taken with subsequent dosing. • Recommendations in Section 4.4 of the SmPC and Section 3 of the PL indicates that patients with impaired vision require assistance from a person with good vision. ***Other risk minimisation measures beyond the Product Information:*** • This medicine will only be available by prescription
Missing information	
Pregnancy and breast-feeding	***Routine risk communication:*** • Lack of experience in this population is mentioned in Section 4.6 of the SmPC (Fertility, pregnancy and lactation). • It is acknowledged that, as a result of potential exposure during breast-feeding, a risk to the newborns/infants cannot be excluded (Section 4.6, SmPC) ***Routine risk minimisation activities recommending specific clinical measures to address the risk****:* • In Section 2 of the PL, patients are encouraged to discuss with a doctor, nurse or pharmacist whether to begin therapy with insulin icodec while pregnant or breast feeding. • It is also advised that a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from insulin icodec therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (Section 4.6, SmPC).

Safety concern	Routine risk minimisation measures
	Other risk minimisation measures beyond the Product Information: • This medicine will only be available by prescription.

Abbreviations: EU-PI = European Union product information ; PL = product leaflet ; SmPC = Summary of Product Characteristics.

5.2 Additional risk minimisation measures

Details of additional risk minimisation measures for medication error in the EU are included in Section 5.2.1.

5.2.1 Additional risk minimisation – Medication errors due to mix-up and during switch from daily basal insulin

Objectives:

To increase the awareness in patients and caregivers regarding the one-time additional dose and the key points of use to minimise the risk of medication errors due to mix-up and during switch from daily basal insulin.

Rationale for the additional risk minimisation activity:

There is a need to introduce the novel dosing regimen including one-time additional dose and weekly dosing frequency to the patients/carers.

Target audience and the planned distribution path:

Novo Nordisk provides educational guide either as digital or hard copies for patients/carers in EU prescribed insulin icodec.

A patient/carer's educational guide will emphasise the following:

For medication errors due to switch from daily basal insulin

- Information on use of one-time additional dose when initiating Awiqli®.
- Key differences between first and second dose.
- Cautionary text on the carton "The pen shows the dose; One step equals 10 units".

For medication errors due to potential mix-up

- Instructions to strictly adhere to weekly dosing regimen.
- Instructions to always check the insulin label before each injection.
- Weekly dosing frequency prominently included on the four faces of the carton.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The process indicators for assessing the effectiveness of information dissemination include tracking the delivery/return of hard copies and downloads of digital educational guides.

The effectiveness indicators include routine pharmacovigilance and safety surveillance activities, types of medication errors reported, and medication error reporting rates.

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

Table 5-2 Pharmacovigilance and risk minimisation activities by safety concern

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None		
Important potential risks		
Medication errors due to mix-up	***Routine risk communication:*** • The risk of mix-ups is presented in Section 4.4 of the SmPC and Section 2 of the PL. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • Instructions for avoidance of medication errors are described in Section 4.4 of the SmPC and Section 2 of the PL • Special precautions for disposal and handling of the pre-filled pen (FlexTouch®) are described in Section 6.6 of the SmPC • Recommendations in Section 4.4 of the SmPC and Section 3 of the PL indicates that patients with impaired vision require assistance from a person with good vision • Product appearance is described in Section 6 of the PL to prevent misidentification of medicine ***Other risk minimisation measures beyond the Product Information:*** • These include differentiation strategy; includes trade name, label text, colour branding of the carton, container label and cartridge holder. • This medicine is only available by prescription. ***Additional risk minimisation measures:*** Additional risk minimisation in the form of patient/carer's educational guide is distributed when insulin icodec is newly launched and made available for the first 2 years to help minimise the risk of medication errors due to mix-up (see Annex 6). The information will describe: • Instructions to strictly adhere to weekly dosing regimen. • Instructions to always check the insulin label before each injection. • Weekly dosing frequency prominently included on the four faces of the carton.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Standardised follow-up questions (see Annex 4A). **Additional pharmacovigilance activities:** None proposed.
Medication errors during switch from daily basal insulin	***Routine risk communication:***	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
	• The risk related to switching from daily basal insulin products is presented in Sections 4.2, 4.4, and 4.9 of the SmPC and Section 2 of the PL ***Routine risk minimisation activities recommending specific clinical measures to address the risk**:* • Instructions for switching from other daily basal insulins to insulin icodec, including a dose calculation table presenting the recommended one-time additional dose and second dose based on the daily basal insulin dosing regimen, are presented in Section 4.2 of the SmPC • Patients must be instructed to check that they inject the correct dose, especially in the first 10 days of treatment (Section 4.4 of the SmPC). It is also indicated in Section 4.2 of the SmPC and Section 2 of the PL that the one-time additional dose is not to be continued with subsequent doses • Patients who are uncertain about the correct dose must be instructed to consult their physician for further guidance (Section 4.4 of the SmPC) • A recommendation to only begin a switch to insulin icodec from another insulin under medical supervision is included in Section 4.4. of the SmPC and Section 2 of the PL • In Section 3 of the PL, switching to insulin icodec is discussed with specific mention that a doctor should prescribe you the first and second dose, and that subsequent doses should be determined in consultation with a doctor • In Section 4.9 of the SmPC, specific warning is included concerning the risk for overdose if the one-time additional dose continues to be taken with subsequent dosing. • Recommendations in Section 4.4 of the SmPC and Section 3 of the PL indicates that patients with impaired vision require assistance from a person with good vision ***Other risk minimisation measures beyond the Product Information:*** This medicine will only be available by prescription. ***Additional risk minimisation measures:*** Additional risk minimisation in the form of patient/carer's educational guide is distributed when insulin icodec is newly launched and made available for the first 2 years to help minimise the risk of medication errors during switch from	Follow-up questions (see Annex 4A). **Additional pharmacovigilance activities:** None proposed

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
	other basal insulin (see Annex 6). The information will describe: • Information on use of one-time additional dose when initiating insulin icodec. • Key differences between first dose and second dose. • Cautionary text on the carton "The pen shows the dose, One step equals 10 units".	
Missing information		
Pregnancy and breast-feeding	***Routine risk communication:*** • Lack of experience in this population is mentioned in Section 4.6 of the SmPC (Fertility, pregnancy and lactation). • It is acknowledged that, as a result of potential exposure during breast-feeding, a risk to the newborns/infants cannot be excluded (Section 4.6, SmPC) ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • In Section 2 in the PL, patients are encouraged to discuss with a doctor, nurse or pharmacist whether to begin therapy with insulin icodec while pregnant or breast feeding. • It is also advised that a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from insulin icodec therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (Section 4.6, SmPC). ***Other risk minimisation measures beyond the Product Information:*** • This medicine will only be available by prescription.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None proposed.

Abbreviations: EU-PI = European Union product information ; PL = product leaflet ; SmPC = Summary of Product Characteristics.

6 Summary of the risk management plan for insulin icodec

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

Awiqli's summary of product characteristics (EU-PI) and its package leaflet give essential information to healthcare professionals and patients on how Awiqli should be used.

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

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

6.1 The medicine and what it is used for

Awiqli is proposed for the treatment of diabetes mellitus in adults. It contains insulin icodec as the active substance and it is given by subcutaneous injection.

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

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

Important risks of Awiqli, together with measures to minimise such risks and the proposed studies for learning more about Awiqli'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 EU-PI 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 minimises its risks.

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

In the case of Awiqli, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant risks, below.

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

6.2.1 List of important risks and missing information

Important risks of Awiqli 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 Awiqli. 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

List of important risks and missing information	
Important identified risks	None
Important potential risks	Medication errors due to mix-up Medication errors during switch from daily basal insulin
Missing information	Pregnancy and lactation

6.2.2 Summary of important risks and missing information

6.2.2.1 Important identified risks

Not applicable, as there are no important identified risks relevant for inclusion in the RMP for Awiqli.

6.2.2.2 Important potential risks

The important potential risks for Awiqli are presented in Table 6-2, and Table 6-3.

Table 6-2 Medication errors due to mix-up

Important potential risk: Medication errors due to mix-up	
Evidence for linking the risk to the medicine	Medication errors are a known risk for many insulin products. Medication errors in clinical trials are systematically collected and the cases are well documented. However, clinical trials are unrepresentative of clinical practice and the appearance of the device (labelling and cartridge colour) are not the same as the marketed device.
Risk factors and risk groups	Patients with diabetes treated with basal–bolus insulin therapy (or other injectable medicine), patients with diabetes living with another person with diabetes, and visually impaired or colour-blind patients may be at a higher risk.
Risk minimisation measures	**Routine risk minimisation measures** ***Routine risk communication:*** • The risk of mix-ups is presented in Section 4.4 of the SmPC and Section 2 of the PL. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • Instructions for avoidance of medication errors are described in Section 4.4 of the SmPC and Section 2 of the PL • Recommendations in Section 4.4 of the SmPC and Section 3 of the PL indicates that patients with impaired vision require assistance from a person with good vision • Product appearance is described in Section 6 of the PL to prevent misidentification of medicine ***Other risk minimisation measures beyond the Product Information:*** • Product differentiation strategy to reduce misidentification; includes trade name, label text, colour branding of the carton, container label and cartridge holder. • This medicine is only available by prescription. ***Additional risk minimisation measures*** Additional risk minimisation measure in the form of patient/carer's educational guide is distributed when insulin icodec is newly launched and made available for the first 2 years to help minimise the risk of medication errors due to mix-up (see Annex 6). The information will describe: • Instructions to strictly adhere to weekly dosing regimen. • Instructions to always check the insulin label before each injection. • Weekly dosing frequency prominently included on the four faces of the carton.

Abbreviations: EU-PI = European Union product information ; PL = product leaflet ; SmPC = Summary of Product Characteristics.

Table 6-3 Medication errors during switch from daily basal insulin

Important potential risk: Medication errors during switch from daily basal insulin	
Evidence for linking the risk to the medicine	For the first injection only, a one-time additional dose of insulin icodec is recommended to be utilised, during the switch to insulin icodec from daily basal insulins (and not for insulin-naïve patients). Incorrect dosing of the one-time additional dose, or following doses, can potentially result in hypoglycaemic events due to overdosing or hyperglycaemic events in the case of underdosing. Completed phase 3a studies using a device in which insulin icodec was used as the investigational drug are the evidence sources of this risk.
Risk factors and risk groups	Patients with diabetes switching from daily basal insulins to insulin icodec represent the most significant risk group. Additionally, as with all injectable insulins using pen delivery systems, patients who have vision impairments may be at a higher risk due to challenges with selecting the correct dose and may require assistance to safely use the pen-injector correctly.

Important potential risk: Medication errors during switch from daily basal insulin	
Risk minimisation measures	**Routine risk minimisation measures** ***Routine risk communication:*** • The risk related to switching from daily basal insulin products is presented in Sections 4.2, 4.4, and 4.9 of the SmPC and Section 2 of the PL ***Routine risk minimisation activities recommending specific clinical measures to address the risk****:* • Instructions for switching from other daily basal insulins to insulin icodec, including a dose calculation table presenting the recommended one-time additional dose and second dose based on the daily basal insulin dosing regimen, are presented in Section 4.2 of the SmPC • Patients must be instructed to check that they inject the correct dose, especially in the first and second injection (Section 4.4 of the SmPC). It is also indicated in Section 4.2 of the SmPC and Section 2 of the PL that the one-time additional dose is not to be continued with subsequent doses • Patients who are uncertain about the correct dose must be instructed to consult their physician for further guidance (Section 4.4 of the SmPC) • A recommendation to only begin a switch to insulin icodec from another insulin under medical supervision is included in Section 4.4. of the SmPC and Section 2 of the PL • In Section 3 of the PL, switching to insulin icodec is discussed with specific mention that a doctor should prescribe you the first and second dose, and that subsequent doses should be determined in consultation with a doctor • In Section 4.9 of the SmPC, specific warning is included concerning the risk for overdose if the one-time additional dose continues to be taken with subsequent dosing. • Recommendations in Section 4.4 of the SmPC and Section 3 of the PL indicates that patients with impaired vision require assistance from a person with good vision ***Other risk minimisation measures beyond the Product Information:*** • This medicine is only available by prescription ***Additional risk minimisation measures*** Additional risk minimisation measure in the form of patient/carer's educational guide is distributed when insulin icodec is newly launched and made available for the first 2 years to help minimise the risk of medication errors during switch from other basal insulin (see Annex 6). The information will describe: • Information on use of one-time additional dose during initiation. • Key differences between first dose and second dose. • Cautionary text on the carton "The pen shows the dose, One step equals 10 units".

Abbreviations: EU-PI = European Union product information ; PL = product leaflet ; SmPC = Summary of Product Characteristics.

6.2.2.3 Missing information .

The missing information for Awiqli is presented in Table 6-4.

Table 6-4 Missing information

Pregnancy and breast-feeding	
Risk minimisation measures	***Routine risk communication:*** • Lack of experience in this population is mentioned in Section 4.6 of the SmPC (Fertility, pregnancy and lactation). • It is acknowledged that, as a result of potential exposure during breast-feeding, a risk to the newborns/infants cannot be excluded (Section 4.6, SmPC) ***Routine risk minimisation activities recommending specific clinical measures to address the risk****:* • In Section 2 of the PL, patients are encouraged to discuss with a doctor, nurse or pharmacist whether to begin therapy with insulin icodec while pregnant or breast feeding. • It is also advised that a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from insulin icodec therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (Section 4.6, SmPC). ***Other risk minimisation measures beyond the Product Information:*** • This medicine is only available by prescription.

Abbreviations: EU-PI = European Union product information ; PL = product leaflet ; SmPC = Summary of Product Characteristics.

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 Awiqli.

6.2.3.2 Other studies in post-authorisation development plan

There are no studies required for Awiqli.

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	No
3	Protocols for proposed and ongoing studies in Categories 1–3 of the section "Summary table of additional pharmacovigilance activities" in RMP Part 3	No
4	Specific adverse event follow-up forms 4A: Proposed follow-up questions for post-marketing surveillance of medication errors	Yes
5	Protocols for proposed and ongoing studies in RMP part IV	No
6	Details of proposed additional risk minimisation measures	Yes
7	Other supporting data (including referenced material)	No
8	Summary of changes to the risk management plan over time	Not applicable

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Annex 4A: Proposed follow-up questions for post-marketing surveillance of medication errors

1 Standard questions concerning medication errors

- Has the patient recently switched from another product (within last 3 months)?
- Is this the first time that the patient is treated for this indication?
- Did the patient experience the same medication error in the past?
- Was the product received in the original packaging? If no, please specify.
- Persons involved in the medication error? (e.g. physician, pharmacist, nurse, patient/caregiver or others?)
- At which stage did the medication error occur?
    - When the product was prescribed by physician.
    - When the product was dispensed, e.g. at pharmacy
    - When the product was prepared to be administered.
    - When the product was administered.
    - An error in the monitoring required to administer the product correctly (e.g. recommendations in the label were not followed).
    - Other (please specify).
- Why do you think the medication Error occurred?
    - Miscalculation of dose
    - Products look alike
- □ Wrong instructions for product use by physician or pharmacist
    - Distraction
    - Drug names alike
    - Insufficient lighting
    - Poor eyesight/colour blindness
    - Insufficient training

- Misunderstanding of product label information (please specify)
- Other (please specify)

- Please describe the reason for the error in your own words
- Did the patient experience any AEs as a consequence of the medication error?
  - If yes, please specify

2 Questions concerning the risk "Medication errors during switch from daily basal insulin"

- When did the medication error occur?
  - Did the medication error happen during switch from daily insulin?
  - Did the medication error take place during the first or the second injection?
- At which stage did the medication error occur?
  - When the product was prescribed by physician.
  - When the product was dispensed, e.g. at pharmacy.
  - When the product was prepared to be administered.
  - When the product was administered.
  - An error in the monitoring required to administer the product correctly (e.g. recommendations in the label were not followed).
  - Other (please specify).
- Why do you think the medication error occurred?
  - Non removal of the one additional dose after first injection
  - Miscalculation of dose
  - Wrong instructions for product use by physician or pharmacist
  - Distraction
  - Poor eyesight/colour blindness/insufficient lighting
  - Insufficient training
  - Misinterpretation of product label information (please specify)

- Other (please specify)

- Please describe the reason for the error in your own words

- Did the patient experience any AE/hypoglycaemic event/hyperglycaemic event as a consequence of the medication error?
  - If yes, please specify, if possible, the severity, seriousness, event outcome, and eventual causal relationship between the event and the medication error

Annex 6: Details of proposed additional risk minimisation measures

Novo Nordisk provides educational guide for patients with diabetes mellitus who are prescribed Awiqli® or their carers.

The educational guide is aimed at increasing awareness about the introduction of the one-time additional dose and describing the key points of use to minimise the risk of medication errors due to mix-up of basal-bolus insulins and during switch from daily basal insulin to once-weekly Awiqli® in diabetes mellitus.

The educational guide is distributed at the time of launch of Awiqli® and is made available as applicable for the first 2 years, to help mitigate the medication errors due to mix up and during switch from daily basal insulin to once-weekly Awiqli®.

The educational guide will be available either as digital or hard copies of patient/carer's guide. The educational guide contains information and instructions related to the following key elements:

Medication errors due to switch from daily basal insulin

- Information on use of one-time additional dose when initiating Awiqli®.
- Key differences between first dose and second dose of Awiqli®.

Medication errors due to mix-up

- Instructions to strictly adhere to weekly dosing regimen as prescribed by the healthcare provider.
- Instructions to always check the insulin label before each injection to avoid accidental mix-ups between Awiqli® and other products.
- Instructions to always use the dose recommended by the healthcare provider.
- Instructions to always use the dose counter and the dose pointer to select the dose. Do not count the pen clicks to select the dose.
- Instructions to check how many units were selected before injecting the weekly insulin.
- Instructions to patients who are blind or have poor vision to always get help/assistance from another person who has good vision and is trained in using the insulin device.

In general

- Instructions to report medication errors or any related side effects and to contact a healthcare provider in case of such events.

Dissemination:

- Relevant components of the educational guide are to be made available in the local language online.
- For patients who prefer hard copy and/or have challenges accessing online material; hardcopy version can be distributed if required, upon agreement with national competent authorities.

Effectiveness:

The effectiveness of the additional risk minimisation activities will be measured by process and effectiveness indicators.

Process indicators will include:

- Tracking of delivery/return of hard copies in countries where needed to assess the effectiveness of information dissemination.
- Tracking the downloads of the educational guide to assess the effectiveness of information dissemination.

Effectiveness indicators will include:

- Routine pharmacovigilance and safety surveillance activities conducted through adverse events monitoring and subsequent documentation in aggregate reports.
- It may be possible to continue the use of the educational guide for Awiqli® beyond 2 years, or discontinue its use earlier, depending on the evaluation of the risk of medication errors.