Risk Management Plan

Insulin degludec/insulin aspart

Active substance(s)	Ryzodeg®
RMP version number:	7.0
Data lock point for this RMP	31 Jan 2018
Date of final sign off:	See signature page
Rationale for submitting an updated RMP	Submission as part of a label update
Summary of significant changes in this RMP	The RMP has been updated using the new template based on the requirements in GVP Module V. A number of changes have been made to the safety specification in accordance with the updated guidelines including the removal of risks that are considered fully characterised and appropriately managed. Furthermore, missing information has been removed as the safety profile of IDegAsp has not been observed to be different in these populations. The RMP has also been updated to include data from the cardiovascular outcomes trial (CVOT) EX1250-4080 (DEVOTE). This trial was conducted as a pre-approval requirement for IDeg and the co-formulation product IDegAsp for the US.
Other RMP versions under evaluation	None
Details of the previously approved RMP	Version number: 6.0 Approved with procedure: EMEA/H/C/002499/II/0017 Date of approval (opinion date): 23 Mar 2017
QPPV Delegate	4.1(b) [redacted]
QPPV Delegate signature	See signature page

[redacted]

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RIMS Change ID: 18006

Abbreviations

ADA	American Diabetes Association
ADR	adverse drug reaction
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BG	blood glucose
BMI	body mass index
CA	congenital anomaly
CI	confidence interval
CV	cardiovascular
CVOT	cardiovascular outcomes trial
DLP	data lock point
DM	diabetes mellitus
EAC	event adjudication committee
EASD	European Association for the Study of Diabetes
EEA	European Economic Area
EMA	European Medicines Agency
ESRD	end-stage renal disease
GFR	glomerular filtration rate
GLP-1	glucagon-like peptide-1
GVP	good pharmacovigilance practices
HR	hazard ratio
IAsp	insulin aspart
IDeg	insulin degludec
IDet	insulin detemir
IFU	instructions for use
IGlar	insulin glargine
INN	international nonproprietary name
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NHANES	National Health and Nutrition Examination Survey
PAD	peripheral arterial disease
PhV	pharmacovigilance
PK	pharmacokinetic
PL	package leaflet
PSUR	periodic safety update report
PT	preferred term
QPPV	qualified person for pharmacovigilance
RMP	risk management plan
RR	reporting rate
s.c.	subcutaneous
SAE	serious adverse event
SmPC	Summary of Product Characteristics
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

1 Product overview

Table 1-1 Product overview

Active substance(s) (INN or common name)	Insulin degludec and insulin aspart
Pharmacotherapeutic group(s) (ATC Code)	A10AD06
Marketing authorisation holder/applicant	Novo Nordisk A/S DK-2880 Bagsværd Denmark Novo Nordisk Inc. 100 College Road West Princeton, NJ 08540 USA
Medicinal products to which this RMP refers	Ryzodeg® FlexTouch® 100 units/mL solution for injection in 3 mL prefilled pen Ryzodeg® Penfill® 100 units/mL solution for injection in 3 mL prefilled cartridge
Invented name(s) in the European Economic Area (EEA)	Ryzodeg®
Marketing authorisation procedure	EU Centralised procedure
Brief description of the product	Ryzodeg® is an insulin product Ryzodeg® – insulin degludec/insulin aspart (IDegAsp) – is a soluble co-formulation of long-acting insulin degludec (IDeg; Tresiba®) and rapid-acting insulin aspart (IAsp) (NovoLog®/NovoRapid®).
	Mode of action: IDeg is a basal insulin that forms soluble multi-hexamers upon s.c. injection, resulting in a depot from which IDeg is continuously and slowly absorbed into the circulation to provide a long and steady action profile. When adding insulin aspart to insulin degludec, the benefits of IDeg with long duration of action and the rapid-acting insulin aspart are combined in 1 injection, with each component acting independently. The combination of the 2 drug substances, IDeg and insulin aspart, provides an action profile with rapid onset of action provided by insulin aspart combined with a flat action profile provided by IDeg. The protracted duration of action of IDeg arises from a modification of human insulin. The amino acid residue threonine in position B30 of human insulin is omitted, and the ε-amino group of lysine in position B29 is coupled to hexadecanedioic acid via a glutamic acid spacer [IDeg; chemical name: LysB29 (Nε-hexadecandioyl-γ-Glu) des(B30) human insulin]. This structure allows IDeg to form soluble and stable multi-hexamers, resulting in a depot in the subcutaneous (s.c.) tissue after injection. The gradual separation of IDeg monomers from the multi-hexamers results in a slow and continuous delivery of IDeg from the s.c. injection site into the circulation, leading to the observed long pharmacokinetic and pharmacodynamic profiles. Furthermore, binding of the fatty acid moiety of IDeg to albumin contributes to some extent to the protraction mechanism. At the target tissues, IDeg monomers bind to and activate insulin receptors, triggering the same cellular effects as human

	insulin, such as promoting glucose uptake. Insulin aspart differs from human insulin in that the proline in position B28 is replaced by aspartic acid. The molecule has fewer tendencies to self-assemble compared to human insulin. Insulin aspart has pH-dependent solubility and an isoelectric point similar to human insulin.
	Ryzodeg® contains IDeg and insulin aspart as active ingredients, glycerol as isotonic agent, phenol and metacresol as antimicrobial preservatives, and zinc and sodium chloride as stabilisers. IDeg and insulin aspart are produced in *Saccharomyces cerevisiae* by recombinant DNA technology. 1 mL solution of Ryzodeg® contains 100 units insulin degludec/insulin aspart* in the ratio 70/30 (equivalent to 2.56 mg insulin degludec and 1.05 mg insulin aspart). Ryzodeg 100 units/mL solution for injection in pre-filled pen One pre-filled pen contains 300 units of insulin degludec/insulin aspart in 3 mL solution.
Hyperlink to the Product Information:	Ryzodeg® PI
Indication(s) in the EEA	**Current** Treatment of diabetes mellitus in adults, adolescents and children from the age of 2 years In patients with type 2 diabetes mellitus, this insulin can be administered alone, in combination with oral antidiabetic medicinal products, and in combination with bolus insulin
	Proposed Not applicable
Dosage in the EEA	**Current** Ryzodeg is to be dosed in accordance with the individual patient's needs. Dose-adjustments are recommended to be primarily based on fasting plasma glucose measurements.
	Proposed Not applicable
Pharmaceutical form(s) and strengths	**Current** Ryzodeg 100 units/mL solution for injection in pre-filled pen Solution for injection (FlexTouch). Ryzodeg 100 units/mL solution for injection in cartridge Solution for injection (Penfill).
	Proposed Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations: EEA = European Economic Area; IDeg = insulin degludec; IDegAsp = insulin degludec/insulin aspart.

2 Safety specification

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

Diabetes is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels. The vast majority of cases of diabetes fall into two broad etiopathogenetic categories. Type 1 diabetes results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. The rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Ultimately, absolute deficiency of insulin secretion will occur. Type 2 diabetes mellitus (T2DM) is a heterogeneous, chronic, progressive disease characterised by a combination of insulin resistance, along with relatively impaired beta-cell function.

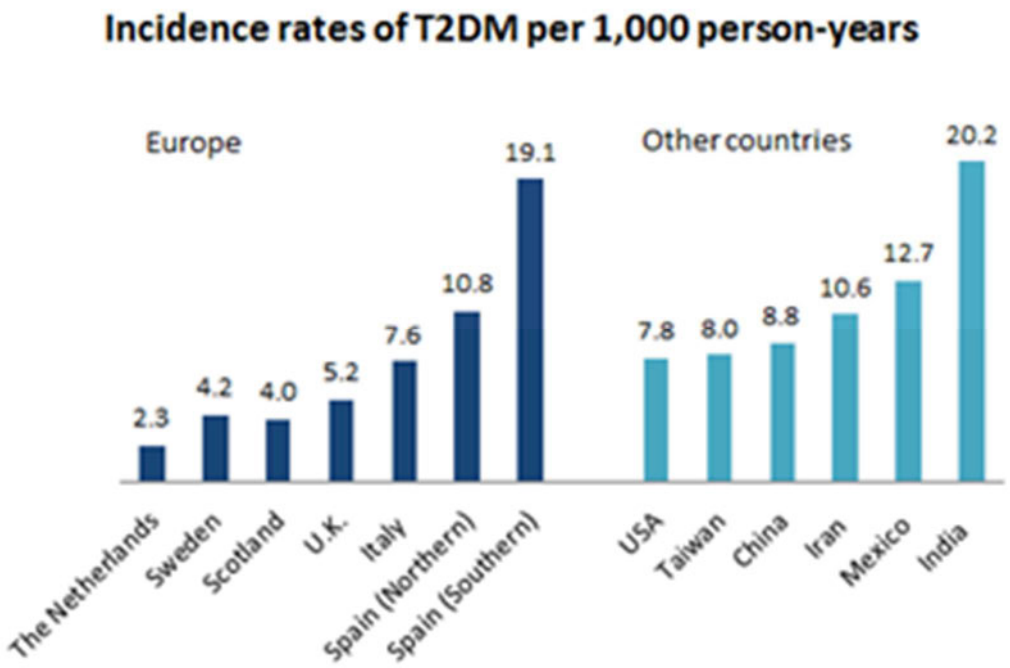
2.1.1 Diabetes mellitus

2.1.1.1 Incidence and prevalence

Incidence

The incidence of T1DM is increasing in both children and adults; the overall annual increase is estimated to be around 3%.[1] In 2015, the International Diabetes Federation (IDF) estimated that worldwide 86,000 children in the age group of 0−14 years develop T1DM annually.[1] In Europe, the incidence ranged from 5.4 per 100,000 children in Romania (2013)[2] to 62.3 in Finland in 2015.[1] In the US, an incidence rate of 27.4 new cases per 100,000 children (0–20 years of age) has been reported.[3]

The incidence rates of T2DM in adults reported in the literature range from 2.3 to 20.2 cases per 1,000 person-years with wide geographical variation, as summarised in Figure 2-1.[4-19]



Abbreviations: T2DM = type 2 diabetes mellitus.

Figure 2-1 Incidence rates of T2DM per 1,000 person years

Prevalence

In 2000, the estimated global prevalence of diabetes was 151 million and it was estimated to rise to 171 million by 2030.[20] In 2015, the estimated prevalence of diabetes was 415 million, representing 8.8% of the world's adult population (aged 20–79 years).[1] If these trends continue, by 2040 approximately 642 million people, or one in 10 adults, are projected to have diabetes. In high-income countries, T2DM constitutes about 87−91% of all diabetes, 7–12% are estimated to have T1DM and 1–3% are estimated to have other types of diabetes.[1] The largest increases are projected to take place in the regions where economies are moving from low to middle-income levels. IDF estimated that globally close to half (46.5%) of all people with diabetes are undiagnosed.[1]

In the IDF region Europe (covering 56 countries and territories), the prevalence of diabetes in the adult population was 9.1% in 2015 (Table 2-1). The countries with the highest prevalence rates of diabetes in the IDF region Europe in 2015 were Malta (13.9%), Portugal (13.6%), Turkey (12.5%) and the Russian Federation (11.1%).[1] Taking the effect of age on prevalence into account, the countries with the highest age-adjusted comparative prevalence rates (standardised to the World population) of diabetes were Turkey (12.8%), Malta (9.9%), Portugal (9.9%) and Cyprus (9.6%).[1]

[1] Countries with estimates based on extrapolation are excluded.

Table 2-1 IDF region-specific estimates of number and prevalence (%) of diabetes mellitus in adults aged 20–79 years in 2015

Region	Population (20–79 years) in millions	Adults with diabetes (20–79 years) in 1,000s [uncertainty range]	Diabetes (20–79 years) regional ('raw') prevalence (%) [uncertainty range]	Diabetes age-adjusted (20–79 years) comparative prevalence (%) [uncertainty range]
Europe	660	59,800.9 [45,082.22–85,563.76]	9.1 [6.83–12.97]	7.3 [5.46–10.93]
World	4,720	414,725.6 [339,377.73–535,877.94]	8.8 [7.19–11.36]	8.8 [7.17–11.33]

Abbreviations: IDF = International Diabetes Federation.

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

T1DM

Worldwide, T1DM is one of the most common endocrine and metabolic conditions and the major type of diabetes in children and young individuals (<20 years of age) worldwide. T1DM most commonly presents in childhood with a peak around the time of puberty, but also peaks in or after the fifth decade, so it may occur at any age.[7, 21] Furthermore, up to 10% of adults initially believed to have T2DM have antibodies associated with T1DM. Beta-cell destruction in adults seems to occur at a much slower rate, often delaying the need for insulin therapy after diagnosis.[22]

Gender

Worldwide, there is a small gender difference in the number of patients with diabetes. There are about 15.6 million more men than women diagnosed with T1DM.[1] However, studies on incidence of T1DM have shown no gender difference in the 0–14-year-old patients and higher incidence among boys than girls older than 15 years.[7, 23]

Ethnicity

There is substantial variation in the incidence of T1DM across ethnic groups. For example, incidence rate of T1DM in children aged <19 years is considered to be the highest among non-Hispanic Whites and the lowest among American Indians.[24]

Based on data from the 2010–2012 National Health Interview Survey and 2012 Indian Health Service's National Patient Information of adults aged 18 years and older, the following age-adjusted prevalence of diagnosed diabetes (T1DM and T2DM combined) by race/ethnicity were reported:[25]

7.6% among Non-Hispanic White
9.0% among Asian Americans
12.8% among Hispanics
13.2% among Non-Hispanic Blacks
15.9% among American Indians and Alaska Native

T2DM

Age

T2DM usually occurs in adults but is increasingly seen in children and adolescents. Age is an important risk factor for T2DM, and the prevalence of T2DM becomes progressively higher with advancing age.[1] Furthermore, the incidence rate for T2DM increases with advancing age until 79 years of age and peaks at ages 70–79 years (in both sexes).[9]

In the IDF region Europe, 30.8% of the general population were aged between 50 and 79 years in 2015 and this is expected to increase to 35.6% by 2040.[1] To a large degree, the high prevalence of T2DM and impaired glucose tolerance are a consequence of ageing of Europe's population.[1]

Gender

In 2015, the IDF Diabetes Atlas reported that there was small gender difference in the global number of people with T2DM worldwide in 2015, and this pattern is projected to continue till 2040. There were about 15.7 million more men than women with diabetes in 2015 (215.2 million men vs. 199.5 million women).[1] In terms of *prevalence*, the NCD Risk Factor Collaboration reported global age-standardised gender-specific diabetes prevalence of 9% (7.2–11.1) in men and 7.9% (6.4–9.7) in women in 2014.[26]

In terms of *incidence*, the incidence rates have been reported to be higher for men than for women in most epidemiological studies.[7, 9, 10, 12]

Ethnic origin

The prevalence of diabetes in the US is one of the highest in the developed world, reflecting not only the high prevalence of obesity but also the significant proportion of the population belonging to high-risk ethnic groups.[27] Ethnic differences in the prevalence of T2DM have been reported based on data from the NHANES cross-sectional survey representative of the US civilian, non-institutionalised population (2011–2012), aged 20 years or older. The following prevalence (age standardised) of diagnosed diabetes mellitus (type unspecified) by ethnicity were reported:

- 7.5% among Non-Hispanic White
- 10.0% among Non-Hispanic Asian
- 15.2% among Non-Hispanic Black
- 12.5% among All Hispanic
- 14.6% among Mexican American[28]

In line with the observed higher incidence of type 2 diabetes among specific ethnic subgroups in the US, several studies in Europe have found that a higher proportion of patients with type 2 diabetes are foreign-born relative to the general population.[29]

2.1.1.3 Risk factors for the disease

Risk factors for T1DM are still being investigated. However, although T1DM mostly occurs in individuals without a family history of the disease, T1DM is highly heritable. The lifetime risk of developing T1DM is 1:20 if a first-line relative has T1DM compared with 1:300 in the general population.[30] Other risk factors may include the presence of certain genes and exposure to specific environmental factors.[31, 32]

Although the exact causes for the development of T2DM are still not known, there are several important risk factors. The most important risk factors are excess body weight, physical inactivity and dietary factors. The rise in the number of people with diabetes worldwide is associated with ageing populations, economic development, increasing urbanisation, less healthy diets and reduced physical activity.[1] Table 2-2 enlists the most important modifiable and non-modifiable risk factors for T2DM.

Table 2-2 Modifiable and non-modifiable risk factors for T2DM[33]

Modifiable risk factors	Non-modifiable risk factors
Overweight or obesity	Age
Physical activity/sedentary behaviour	Sex
Dietary factors	Ethnicity
Smoking	Family history of T2DM
Previously identified (impaired) glucose tolerance (IGT and/or IFG)	History of gestational diabetes
Abnormal lipids (elevated triglycerides, low HDL cholesterol levels)	Polycystic ovary syndrome
Hypertension	
Inflammation	
Intrauterine environment	

Abbreviations: HDL = high-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2DM = type 2 diabetes mellitus.

2.1.1.4 The main existing treatment options

The main treatment options for T1DM and T2DM follow the recommendations in the European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) treatment guidelines:[34] Glucose control remains a major focus in the management of patients with type 2 diabetes. However, this should always be in the context of a comprehensive cardiovascular risk factor reduction programme, to include smoking cessation and the adoption of other healthy lifestyle habits, blood pressure control and lipid management.

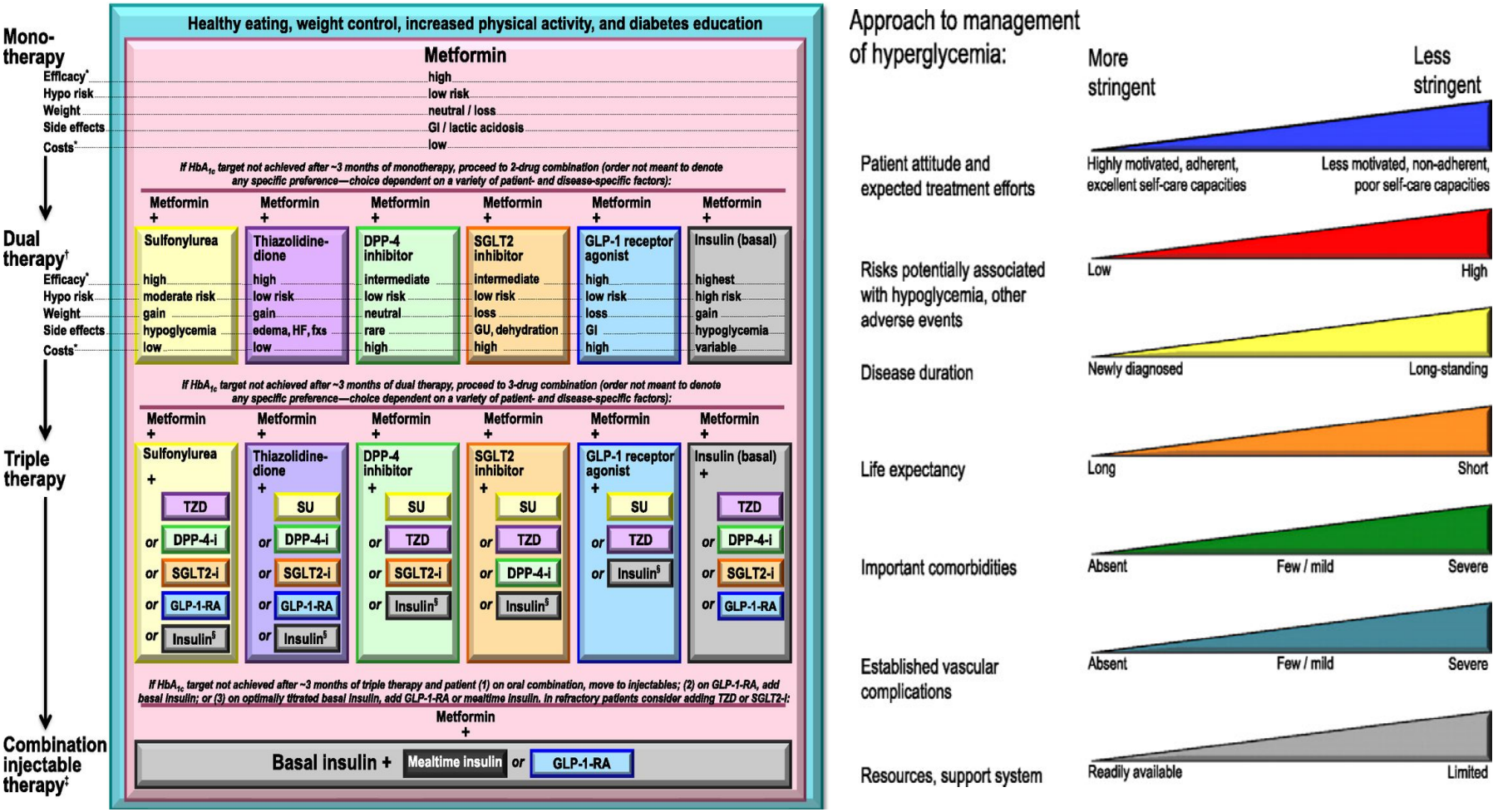
T1DM[34]

1. Multiple-dose insulin injections or continuous subcutaneous insulin injection
2. Regular HbA_{1c} testing
3. Carefully calculated diet and planned physical activity
4. Home blood glucose (BG) testing as appropriate

Although diet and exercise are important in the treatment of T1DM, they do not reverse the disease or remove the need for insulin.

T2DM[34]

Figure 2-2 shows the anti-hyperglycaemic therapy in type 2 diabetes as recommended by the ADA and EASD: general recommendations. Potential sequences of anti-hyperglycaemic therapy for patients with type 2 diabetes are displayed, the usual transition being vertical, from top to bottom. In addition, the ADA and EASD recommends individualised treatment targets for HbA_{1c} based on the patient and the disease features.



Abbreviations: ADA = American Diabetes Association; DPP-4 = dipeptidyl peptidase-4; EASD = European Association for the Study of Diabetes; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycosylated haemoglobin; RA = receptor agonist; SGLT2 = sodium-glucose co-transporter-2; SU = sulphonylurea; TZD = thiazolidinedione.

Figure 2-2 Anti-hyperglycaemic therapy and the approach to management of hyperglycaemia in type 2 diabetes as recommended by the ADA and EASD

2.1.1.5 Natural history of the indicated condition including mortality and morbidity

Natural history of the disease – T1DM

The natural history of T1DM is initiation of β-cell autoimmunity that eventually may destroy all β-cells, resulting in a progressive and predicable loss in insulin secretory function. T1DM does not present until the majority of β-cells are destroyed as there is a gap between the onset of autoimmunity and the onset of diabetes.[35] When a patient starts on insulin injections, the pancreas is under less pressure to produce insulin, which stimulates the pancreas to produce insulin from the remaining β-cells. However, after a period of months, the vast majority of these remaining β-cells are destroyed, and the pancreas stops producing sufficient insulin to aid BG control. Recently, some aspects of this classical way of thinking about T1DM have been modified as it has been shown that pancreatic β-cells may persist in some T1DM individuals for an extended period of time.[36] T1DM can affect major organs in your 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.

Natural history of the disease – T2DM

T2DM is a heterogeneous, chronic, progressive disease characterised by insulin resistance, along with relatively impaired pancreatic β-cell function. While the course of the disease is variable, it usually follows a predictable progression. In the early stages, individuals with T2DM 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 β-cells gradually lose their ability to secrete insulin (β-cell insufficiency), eventually leading to a state of insulin dependency.[37]

The endpoint of the disease process, insulin deficiency, can be absolute or relative in the coexistence of insulin resistance (response of target tissues, such as muscle, liver and adipose tissue, to insulin). The result is chronic hyperglycaemia, caused by reduced insulin secretion, decreased insulin utilisation and increased liver glucose production, which in the long run lead to diabetic complications. Diabetes is a leading cause of end-stage renal disease (ESRD), non-traumatic lower extremity amputations, adult blindness and cardiovascular complications.[37-39]

Mortality

Diabetes and its complications are major causes of early death in most countries. Estimates of the number of deaths caused annually by diabetes on a global scale are subject to uncertainty, owing in part to the fact that diabetes is often omitted from death certificates as the cause of death and that diabetes-related mortality data are lacking in many countries. Based on the IDF Atlas, it has been estimated that in 2015, approximately 5.0 million deaths in people in the age group 20−79 years may have been attributable to diabetes. Diabetes accounted for 14.5% of global all-cause mortality

among people in this age group. Close to half (46.6%) of the deaths due to diabetes were in people <60 years.[1]

The World Health Organization (WHO) has estimated that in 2012 there were 1.5 million deaths worldwide directly caused by diabetes. It was the eighth leading cause of death among both sexes and the fifth leading cause of death in women in 2012.[40] High blood glucose age-standardised mortality rates, accounting for differences in population structure, are highly variable across WHO regions. Rates (per 100,000 by WHO region, age ≥20 years) are highest in the WHO Eastern Mediterranean, South-East Asia and African Regions and much lower in the remaining regions such as in the European Region.[40]

A Swedish register-based study reported an excess risk of all-cause mortality and cardiovascular death in patients with T2DM compared to general population with an adjusted hazard ratio (HR) of 1.15 $[1.14;1.16]_{95\%\ CI}$ and 1.14 $[1.13;1.15]_{95\%\ CI}$, respectively.[41] Cardiovascular disease is one of the leading causes of death among people with diabetes and can account for ≥50% of deaths due to diabetes in some populations.[1] For instance, heart failure survival is worse in the presence of diabetes.[42] Moreover, mortality after a first myocardial infarction (MI) has remained significantly higher in the diabetic population, in spite of improved survival in both diabetic and non-diabetic patients with incident MI over the past decades.[43-45] Furthermore, cancer patients with diabetes have poorer survival than cancer patients without diabetes (meta-analyses of 23 studies: HR = 1.41 $[1.28,1.55]_{95\%\ CI}$).[46] Also, higher cancer mortality rates have been observed in patients with diabetes than non-diabetic patients (meta-analysis of 12 studies: RR = 1.16 $[1.03;1.30]_{95\%\ CI}$).[47] In patients with T2DM, cancer-specific mortality shows significantly increased HRs in particular for liver, pancreatic, ovary and colorectal cancer.[48]

2.1.1.6 Important co-morbidities found in the target population

Important co-morbidities of diabetes are shown in Table 2-3.

Table 2-3 Important co-morbidities of diabetes

Important co-morbidity category	Important co-morbidity sub-category
Macrovascular complications	Congestive heart failure Myocardial infarction Peripheral arterial disease Stroke
Microvascular complications	Nephropathy Peripheral neuropathy Retinopathy Extremity ulcers
Cancer	Overall cancer Liver Pancreatic Colorectal

2.2 Module SII: Nonclinical safety findings

2.2.1 Important nonclinical safety findings and their relevance to human use

Nonclinical safety was assessed in the completed nonclinical studies on the mono-components and in a 13-week repeated dose toxicity study and an embryo–fetal development study both in rats on the IDegAsp combination. The studies confirmed hypoglycaemia as an important nonclinical safety finding. The effect on embyro–fetal development was considered secondary to hypoglycaemia, and without toxicological significance.

Table 2-4 Important nonclinical safety findings and their relevance to human use

Key safety findings (from nonclinical studies)	Relevance to human use
General toxicity studies Hypoglycaemia	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. The effect of Ryzodeg® was similar to what was observed following the administration of Tresiba® alone.
Reproductive toxicity Effects were similar to those from dosing with NPH insulin, including minor skeletal changes in the offspring.	All effects were considered secondary changes to the effect on the maternal blood glucose levels (hypoglycaemia), and without toxicological significance.
Carcinogenicity studies No carcinogenic potential was shown in rats dosed for 52 weeks.	All studies support the conclusion that the carcinogenic potential of Tresiba® is similar to that of human insulin.
Mitogenicity studies The mitogenic/metabolic potency ratio 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 Some rats developed antibodies against Tresiba® or insulin aspart during repeated-dose toxicity studies.	Antibody formation against Tresiba® or insulin aspart could result in lack of efficacy. The development of antibodies tended to be lower than that observed for NPH insulin in the same studies. Antibody formation in animals is not considered predictive for humans.
Injection site tolerability Local tissue reactions after single or repeated s.c. administration of Tresiba® and Ryzodeg® were mild and similar to those of the vehicle or NPH insulin.	No safety concerns raised

Key safety findings (from nonclinical studies)	Relevance to human use
General safety pharmacology No *in vitro* inhibition of potassium channels (hERG), binding or effect on action potential in rabbit-isolated cardiac Purkinje fibres was observed. No effect on cardiovascular function (blood pressure, heart rate and QT interval) was observed in telemetered conscious and glucose-clamped anaesthetised dogs.	No safety concerns raised
Mechanisms for drug interactions Tresiba® showed low potential for drug–drug interactions in the nonclinical studies. Common protein-bound drugs (e.g., ibuprofen, warfarin, acetylsalicylate, salicylate, palmitate, oleate, linoleate, and the frequently used antidiabetic agents glimepiride, metformin, sitagliptin and liraglutide) did not affect the binding of Tresiba® to human serum albumin at therapeutically/physiologically relevant drug concentrations, and protein-binding interaction is considered unlikely.	No safety concerns raised

Abbreviations: NPH = neutral protamine Hagedorn; PD = pharmacodynamics.

2.2.2 Conclusions on nonclinical data

In summary, only the important identified risk of hypoglycaemia was confirmed by clinical data and there were no important potential risks or important missing information that arose from safety concerns from the nonclinical data; see Table 2-5.

Table 2-5 Nonclinical summary of safety concerns

Safety concerns
Important identified risks (confirmed by clinical data) Hypoglycaemia
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

Table 2-6 to Table 2-9 detail the clinical trial exposure to IDegAsp in which IDegAsp was used as the primary investigational drug. In addition, Table 2-7 details the exposure to IDeg in trial EX1250-4080 (DEVOTE). This trial was conducted as a pre-approval requirement for IDeg and the co-formulation product IDegAsp for the US. It was a double-blind, randomised, controlled, treat-to-target trial performed to confirm the cardiovascular safety of IDeg compared to insulin glargine (IGlar; 100 units/mL), when added to standard-of-care in subjects with T2DM at high risk of cardiovascular events. The trial was event driven and continued until a pre-specified minimum number of EAC-confirmed major adverse cardiovascular events (MACEs; comprising cardiovascular death, non-fatal MI or non-fatal stroke) were accrued.

Table 2-6 Duration of exposure

Population/ Indication	Duration	IDegAsp (N)	IDeg (N)	Other comparator (N)
T1DM	>= 0 month	543		359
	>= 1 month	533		351
	>= 2 months	520		344
	>= 3 months	510		339
	>= 4 months	332		163
	>= 5 months	324		160
	>= 6 months	321		157
	>= 7 months	252		120
	>= 8 months	249		120
	>= 9 months	245		118
	>= 10 months	243		118
	>= 11 months	238		116
	>= 12 months	235		114
T2DM	>= 0 month	2780	155	1668
	>= 1 month	2700	147	1616
	>= 2 months	2593	142	1542
	>= 3 months	2556	139	1515
	>= 4 months	2282	137	1358
	>= 5 months	2189	135	1293
	>= 6 months	2146	133	1259
	>= 7 months	212	1	220
	>= 8 months	206		219
	>= 9 months	204		216
	>= 10 months	202		214
	>= 11 months	198		213
	>= 12 months	194		213
All subjects	>= 0 month	3323	155	2027
	>= 1 month	3233	147	1967
	>= 2 months	3113	142	1886
	>= 3 months	3066	139	1854
	>= 4 months	2614	137	1521
	>= 5 months	2513	135	1453
	>= 6 months	2467	133	1416
	>= 7 months	464	1	340
	>= 8 months	455		339
	>= 9 months	449		334
	>= 10 months	445		332
	>= 11 months	436		329
	>= 12 months	429		327

N: Number of subjects
Cumulative reporting period DIBD to 31-Jan-2018
One month is calculated as 30.5 days.
Completers in 6 weeks, 16 weeks, 26 weeks, 52 weeks trials count as having 1.4 months, 3.7 months, 6 months, 12 months exposure respectively
Trials included:
NN5401-1791, NN5401-1792, NN5401-3570, NN5401-3590-3726, NN5401-3592, NN5401-3593, NN5401-3594-3645 NN5401-3597, NN5401-3598, NN5401-3816, NN5401-3844, NN5401-3896, NN5401-3940, NN5401-3941 NN5401-3996, NN5401-4003, NN5401-4243

nn1250/nn1250-rmp/rmp_ryzodeg_20180516_er
16MAY2018:15:47:49 - t_expo_idegasp_conf_months.sas/t_expo_idegasp_conf_months.txt

Table 2-7 Exposure and observation time – By subgroups in trial EX1250-4080 (DEVOTE)

			IDeg	IGlar	Total
Sex	Males	N	2396	2382	4778
		PYE (years)	4298	4249	8547
		PYO (years)	4756	4717	9473
	Females	N	1422	1437	2859
		PYE (years)	2493	2481	4975
		PYO (years)	2811	2841	5652
Sex*age	Males 75 years or older	N	234	263	497
		PYE (years)	412	447	859
		PYO (years)	461	505	966
	Males 65 years or older	N	1245	1260	2505
		PYE (years)	2242	2244	4486
		PYO (years)	2478	2491	4969
	Females 75 years or older	N	147	175	322
		PYE (years)	246	292	537
		PYO (years)	292	341	633
	Females 65 years or older	N	738	712	1450
		PYE (years)	1288	1241	2530
		PYO (years)	1456	1410	2866
Renal status	Severe renal impairment	N	108	106	214
		PYE (years)	178	180	358
		PYO (years)	210	202	412
	Moderate renal impairment	N	1321	1383	2704
		PYE (years)	2345	2431	4776
		PYO (years)	2615	2730	5345
	Mild renal impairment	N	1596	1522	3118
		PYE (years)	2866	2702	5568
		PYO (years)	3183	3026	6209

			IDeg	IGlar	Total
Hepatic status	Hepatic impairment	N	102	94	196
		PYE (years)	163	141	303
		PYO (years)	199	168	368
Cardiac impairment	Established CVD/CKD	N	3265	3244	6509
		PYE (years)	5824	5715	11538
		PYO (years)	6490	6424	12915
	Risk factors for CVD	N	538	567	1105
		PYE (years)	951	1008	1959
		PYO (years)	1050	1121	2171
Race	White	N	2903	2872	5775
		PYE (years)	5208	5116	10325
		PYO (years)	5793	5733	11526
	Black or African American	N	401	431	832
		PYE (years)	680	716	1397
		PYO (years)	787	836	1624
	Asian	N	391	385	776
		PYE (years)	693	678	1371
		PYO (years)	749	737	1486
	Native Hawaiian or Other Pacific Islander	N	11	13	24
		PYE (years)	17	24	41
		PYO (years)	20	25	45
	Other	N	94	104	198
		PYE (years)	165	174	339
		PYO (years)	185	200	385

N: Number of subjects, PYE: Patient years of exposure, PYO: Patient years of observation
Mild renal impairment: 60 <= eGFR < 90 mL/min/1.73m2 per CKD-EPI
Moderate renal impairment: 30 <= eGFR < 60 mL/min/1.73m2 per CKD-EPI
Severe renal impairment: eGFR < 30 mL/min/1.73m2 per CKD-EPI
CVD: Cardiovascular disease, CKD: Chronic kidney disease

Table 2-8 Exposure by indication, age group and gender

		IDegAsp N (SYE)			IDeg N (SYE)			Other comparator N (SYE)		
Population	Age range	Male	Female	Total	Male	Female	Total	Male	Female	Total
T1DM	Infants (29 days-23 months)	0	0	0	0	0	0	0	1 (<1)	1 (<1)
	Children (24 months-12 years)	59 (18)	60 (18)	119 (36)	0	0	0	55 (16)	58 (18)	113 (34)
	Adolescents (13-17 years)	29 (9)	33 (10)	62 (19)	0	0	0	30 (9)	35 (10)	65 (20)
	Adults (18-65 years)	186 (159)	169 (133)	355 (292)	0	0	0	77 (66)	92 (71)	169 (136)
	Elderly (66-74 years)	1 (1)	2 (1)	3 (1)	0	0	0	3 (3)	6 (5)	9 (7)
	Elderly (75-84 years)	2 (2)	2 (2)	4 (4)	0	0	0	2 (2)	0	2 (2)
	Total	277 (188)	266 (163)	543 (352)	0	0	0	167 (96)	192 (103)	359 (199)
T2DM	Adults (18-65 years)	1166 (565)	989 (484)	2155 (1050)	74 (33)	48 (22)	122 (56)	693 (360)	584 (305)	1277 (665)
	Elderly (66-74 years)	296 (138)	245 (114)	541 (252)	18 (9)	9 (4)	27 (13)	188 (86)	153 (72)	341 (158)
	Elderly (75-84 years)	39 (16)	42 (21)	81 (37)	4 (2)	2 (1)	6 (2)	28 (13)	21 (10)	49 (23)
	Elderly (85+ years)	2 (1)	1 (<1)	3 (1)	0	0	0	1 (<1)	0	1 (<1)
	Total	1503 (720)	1277 (620)	2780 (1340)	96 (44)	59 (27)	155 (71)	910 (459)	758 (387)	1668 (846)
All subjects	Infants (29 days-23 months)	0	0	0	0	0	0	0	1 (<1)	1 (<1)
	Children (24 months-12 years)	59 (18)	60 (18)	119 (36)	0	0	0	55 (16)	58 (18)	113 (34)
	Adolescents (13-17 years)	29 (9)	33 (10)	62 (19)	0	0	0	30 (9)	35 (10)	65 (20)
	Adults (18-65 years)	1352 (724)	1158 (617)	2510 (1341)	74 (33)	48 (22)	122 (56)	770 (426)	676 (375)	1446 (801)
	Elderly (66-74 years)	297 (138)	247 (115)	544 (253)	18 (9)	9 (4)	27 (13)	191 (88)	159 (77)	350 (165)
	Elderly (75-84 years)	41 (18)	44 (23)	85 (41)	4 (2)	2 (1)	6 (2)	30 (15)	21 (10)	51 (25)
	Elderly (85+ years)	2 (1)	1 (<1)	3 (1)	0	0	0	1 (<1)	0	1 (<1)

Cumulative reporting period to 31-Jan-2018, N: Number of subjects, SYE: Subject years of exposure
Clinical pharmacology trials included: NN1045-3834, NN1050-4008, NN5401-1738, NN5401-1788, NN5401-1790, NN5401-1959, NN5401-1977, NN5401-1984 NN5401-1978, NN5401-1979, NN5401-1980, NN5401-1981, NN5401-1982, NN5401-1983, NN5401-1985, NN5401-3539, NN5401-3857
Exploratory/confirmatory trials included: NN5401-3594-3645, NN5401-3816, NN5401-1791, NN5401-1792, NN5401-3570, NN5401-3590-3726, NN5401-3592, NN5401-3593, NN5401-3597, NN5401-3598, NN5401-3844, NN5401-3896, NN5401-3940, NN5401-3941-4003, NN5401-3996, NN5401-4243
Other comparator: BIAsp, IDet, IGlar, Mix30

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Table 2-9 Total exposure by ethnic or racial origin

Population	Other Racial group	IDegAsp N (SYE)	IDeg N (SYE)	comparator N (SYE)
T1DM	Asian Indian	1 (1)	0	1 (<1)
	Asian non-Indian	3 (2)	0	3 (2)
	Black or African American	18 (10)	0	10 (6)
	White	499 (325)	0	327 (180)
	Native Hawaiian or Other Pacific Islander	1 (1)	0	1 (1)
	Not Applicable	15 (11)	0	8 (5)
	Other	6 (3)	0	9 (4)
	Total	543 (352)	0	359 (199)
T2DM	Asian	436 (203)	0	260 (117)
	Asian Indian	180 (94)	1 (<1)	161 (92)
	Asian non-Indian	594 (288)	8 (4)	372 (181)
	American Indian or Alaska Native	1 (<1)	0	0
	Black or African American	109 (61)	8 (3)	30 (18)
	White	1409 (682)	138 (63)	800 (428)
	Japanese	33 (4)	0	32 (4)
	Native Hawaiian or Other Pacific Islander	2 (1)	0	1 (1)
	Other	16 (7)	0	12 (5)
	Total	2780 (1340)	155 (71)	1668 (846)
All subjects	Asian	436 (203)	0	260 (117)
	Asian Indian	181 (95)	1 (<1)	162 (92)
	Asian non-Indian	597 (289)	8 (4)	375 (184)
	American Indian or Alaska Native	1 (<1)	0	0
	Black or African American	127 (71)	8 (3)	40 (24)
All subjects	White	1908 (1007)	138 (63)	1127 (609)
	Japanese	33 (4)	0	32 (4)
	Native Hawaiian or Other Pacific Islander	3 (2)	0	2 (2)
	Not Applicable	15 (11)	0	8 (5)
	Other	22 (10)	0	21 (9)
	Total	3323 (1692)	155 (71)	2027 (1046)

Cumulative reporting period to 31-Jan-2018, N: Number of subjects, SYE: Subject years of exposure
Not Applicable: Subjects from countries which did not allow reporting of race.
Clinical pharmacology trials included: NN1045-3834, NN1050-4008, NN5401-1738, NN5401-1788, NN5401-1790, NN5401-1959, NN5401-1977, NN5401-1984
NN5401-1978, NN5401-1979, NN5401-1980, NN5401-1981, NN5401-1982, NN5401-1983, NN5401-1985, NN5401-3539, NN5401-3857
Exploratory/confirmatory trials included: NN5401-3594-3645, NN5401-3816, NN5401-1791, NN5401-1792, NN5401-3570, NN5401-3590-3726,
NN5401-3592, NN5401-3593, NN5401-3597, NN5401-3598, NN5401-3844, NN5401-3896, NN5401-3940, NN5401-3941-4003, NN5401-3996, NN5401-4243
Other comparator: BIAsp, IDet, IGlar, Mix30

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2.4 Module SIV: Populations not studied in clinical trials

2.4.1 Exclusion criteria in pivotal clinical trials within the development programme

The main exclusion criteria in the IDegAsp clinical development programme are listed in Table 2-10.

Table 2-10 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Proliferative retinopathy requiring acute treatment or maculopathy according to the investigator's opinion	Intensification of insulin therapy with abrupt improvement of glycaemic control can result in worsening of retinopathy.	No Worsening of retinopathy is a well-established effect of insulins when blood glucose is lowered rapidly. It is standard clinical practice to titrate insulin dose slowly when a patient has retinopathy requiring treatment.
Recurrent severe hypoglycaemia (more than 1 severe hypoglycaemic episode during the last 12 months) or hypoglycaemic unawareness or hospitalisation for diabetic ketoacidosis during the previous 6 months	Patients with recurrent severe hypoglycaemia or hypoglycaemic unawareness or recent hospitalisation for diabetic ketoacidosis may find it difficult to adhere to a treat-to-target insulin regimen. Hypoglycaemic unawareness is a safety concern when patients are enrolled in studies with a treat-to-target strategy. These patients are better treated on an individual basis.	No There is no indication that this population would respond differently to IDegAsp when treated on an individual basis compared to the general population.
Uncontrolled treated/untreated severe hypertension (systolic blood pressure ≥180 mm mercury [Hg] and/or diastolic blood pressure ≥100 mmHg)	Patients with uncontrolled treated/untreated severe hypertension are at increased risk of developing cardiovascular disease. In accordance with ADA recommendations, these patients require aggressive treatment to lower BP.	No There is no indication that this population of patients would respond differently to IDegAsp than the general population.

Abbreviations: ADA = American Diabetes Association; BP = blood pressure; IDegAsp = insulin degludec/insulin aspart.

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 2-11 details the exposure to IDegAsp in special populations.

Table 2-11 Exposure to IDegAsp in special populations – Non-paediatric

Population/ Indication	Special population	N (SYE)
Clinical pharmacology trials		
Healthy	Pregnant women	N/A
	Lactating women	N/A
	Renal impairment	
	Mild	5
	Moderate	N/A
	Severe	N/A
	Hepatic impairment	N/A
	Cardiac impairment	N/A
	Sub-populations with genetic polymorphism	N/A
	Immunocompromised	N/A
T1DM	Pregnant women	1
	Lactating women	N/A
	Renal impairment	
	Mild	26
	Moderate	3
	Severe	N/A
	Hepatic impairment	2
	Cardiac impairment	N/A
	Sub-populations with genetic polymorphism	N/A
	Immunocompromised	N/A
T2DM	Pregnant women	N/A
	Lactating women	N/A
	Renal impairment	
	Mild	9
	Moderate	N/A
	Severe	N/A
	Hepatic impairment	N/A
	Cardiac impairment	N/A
	Sub-populations with genetic polymorphism	N/A
	Immunocompromised	N/A

Exposure to IDegAsp in special populations - non-pediatric

Population/ Indication	Special population	N (SYE)
Therapeutic exploratory and other + confirmatory trials		
T1DM	Pregnant women	3 (2)
	Lactating women	N/A
	Renal impairment	
	Mild	63 (49)
	Moderate	8 (6)
	Severe	N/A
	Hepatic impairment	2 (1)
	Cardiac impairment	N/A
	Sub-populations with genetic polymorphism	N/A
	Immunocompromised	N/A
T2DM	Pregnant women	1 (0)
	Lactating women	N/A
	Renal impairment	
	Mild	694 (328)
	Moderate	175 (79)
	Severe	1 (1)
	Hepatic impairment	14 (6)
	Cardiac impairment	N/A
	Sub-populations with genetic polymorphism	N/A
	Immunocompromised	N/A

N: Number of subjects
Cumulative reporting period to 31-Jan-2018, SYE: Subject years of exposure, N/A: Not applicable
Clinical pharmacology trials included: NN1045-3834, NN1050-4008, NN5401-1738, NN5401-1788, NN5401-1790, NN5401-1959, NN5401-1977, NN5401-1984
NN5401-1978, NN5401-1979, NN5401-1980, NN5401-1981, NN5401-1982, NN5401-1983, NN5401-1985, NN5401-3539, NN5401-3857
Exploratory/confirmatory trials included: NN5401-3594-3645, NN5401-3816, NN5401-1791, NN5401-1792, NN5401-3570, NN5401-3590-3726,
NN5401-3592, NN5401-3593, NN5401-3597, NN5401-3598, NN5401-3844, NN5401-3896, NN5401-3940, NN5401-3941-4003, NN5401-3996, NN5401-4243
Hepatic impairment was classified by a total bilirubin plus albumin score > 2.
For bilirubin (µmol/l), if value < 34.2 then bilirubin score = 1.
if 34.2 <= value <= 51.3 then bilirubin score = 2 and if value > 51.3 then
bilirubin score = 3. For albumin (g/l), if value > 35 then albumin score = 1;
if 28 <= value <= 35 then albumin score = 2; if value < 28 then albumin score = 3.
Mild renal impairment was defined by having estimated creatinine clearance GFR between 60 and 89.
Moderate renal impairment was defined by having estimated creatinine clearance GFR between 30 and 59
Severe renal impairment was defined by having estimated creatinine clearance GFR under 30.
Creatinine clearance and renal impairment level are values calculated at baseline.
Creatinine clearance GFR calculated as below based on age and body weight at randomisation
Male: ((140-age (yrs)) * body weight (kg)) / (72 * creatinine serum (mg/dL))
Female: ((140-age (yrs)) * body weight (kg) * 0.85) / (72 * creatinine serum (mg/dL))
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2.4.3.1 Patients with hepatic impairment

A total of 18 subjects with mild to moderate hepatic impairment (classified according to the Child–Pugh Classification) have been exposed to IDegAsp in all completed clinical trials (see Table 2-11). However, a further 82 subjects with hepatic impairment were exposed to IDeg (the basal component of IDegAsp) in the main clinical development programme. A further 102 subjects with hepatic impairment were exposed to IDeg in trial EX1250-4080 (DEVOTE) (see Table 2-7).

2.4.3.2 Patients with renal impairment

Severe renal impairment was an exclusion criteria for the main clinical trial programmes of IDeg and IDegAsp. However a total of 983 subjects with mild to moderate renal impairment have been exposed to IDegAsp throughout the clinical trial programme (see Table 2-11). A further 3,025 subjects with renal impairment were exposed to IDeg in the CVOT trial EX1250-4080 (DEVOTE) (Table 2-7). This included 1,321 subjects with moderate (defined as glomerular filtration rate [GFR] of 30–59 mL/min/1.73 m^2 per CKD-Epi), and 108 subjects with severe renal impairment (defined as GFR <30 mL/min/1.73 m^2 per CKD-Epi).

2.4.3.3 Patients with cardiovascular disease

Trial EX1250-4080 (DEVOTE) was designed to confirm the cardiovascular safety of IDeg relative to IGlar in a population of subjects with T2DM at high risk of cardiovascular events. Eighty-five per cent (85%) of the subjects randomised had prior cardiovascular disease or chronic kidney disease. The remainder of patients had multiple cardiovascular risk factors. This resulted in 3,265 subjects with established cardiovascular disease and 538 subjects with multiple CV risk factors being exposed to IDeg. This trial confirmed the cardiovascular safety of IDeg.

2.5 Module SV: Post-authorisation experience

2.5.1 Post-authorisation exposure

2.5.1.1 Method used to calculate exposure

Exposure from post-marketing use has been calculated from sales figures, including samples, of IDegAsp released from Novo Nordisk to external customers up to the data lock point (DLP) of this RMP. Exposure has been derived from the total volume in units (U) of Ryzodeg® sold, assuming an average daily consumption of 40 U. As the estimated exposure is based on volume distributed to external customers and average daily usage rather than actual patient exposure, the numbers may be over- or underestimated.

2.5.1.2 Exposure

Estimates of accumulated exposure to IDegAsp from post-authorisation experience since marketing authorisation are shown in Table 2-12. (These figures include samples.)

Table 2-12 Estimated patient-years of exposure from post-authorisation experience

Patient-years of exposure (PYE)					
Europe*	**China**	**Japan**	**US**	**Rest of the World**	**Total**
12,800	**10**	**61,845**	**0**	**94,238**	**168,893**

*Europe includes all EU countries as well as Norway, Iceland, Liechtenstein and Switzerland.

Abbreviations: PYE = patient-years of exposure.

2.5.2 Post-authorisation use and off-label use

IDegAsp is a prescription-only medicine and which reduces the potential for off-label use. However, the possibility of off-label use cannot be excluded. Novo Nordisk performs regular standardised searches in the safety database to identify cases concerning off-label use of IDegAsp (see Table 2-13).

Table 2-13 Reporting pattern of cases related to off-label use, up until 31 Jan 2018

Type of case reports	N (RR)
Pregnancy	14 (N/A)
Off-label use using standardised search criteria[a]	43 (0.03)

[a]By using PTs Contraindicated drug administered, Device use issue, Drug administered to patient of inappropriate age, Intentional product use issue, Off label use, Off label use of device, Product use issue and Prescription drug used without a prescription. Cases concerning potential off-label use of Ryzodeg® in pregnant and lactating women have been identified from the Novo Nordisk safety database by using specific searches. Reporting rate for pregnancy and lactation cases cannot be calculated as it is not possible to estimate post-marketing exposure by sub-populations because exposure estimates are based on total sales volume and not on prescription data.

Reporting rate is calculated as valid cases per 100 PYE.

Abbreviations: N = number of cases; N/A = not applicable; RR = reporting rate; PT = preferred term; PYE = patient-years of exposure; RR = reporting rate.

Of the 43 cases reported to date, 11 were associated with co-reported AEs, 2 of which were classified as serious. These 2 SAEs were reported in the same case under the PTs Device failure and High blood glucose. Neither of these cases were considered to change the current safety profile of IDegAsp. The case reports retrieved using the standardised search criteria were mostly regarding the off-label use of IDegAsp in an unauthorised dosing regimen (~49%) and in paediatric populations from countries where the product is not approved in this population (~28%).

Cumulatively, 14 case reports were received concerning off-label use of IDegAsp in pregnant women. The foetal outcome in 6 reports was reported as ‘live birth without CA’. One (1) case report concerning the use of IDegAsp in a 32-year-old pregnant woman was reported with spontaneous abortion. The patient underwent medical termination of the pregnancy due to a foetal anomaly (unspecified). The patient had a medical history of hypertension and an obstetric history of previous pregnancy which did not result in live birth. The outcome of the remaining 7 pregnancies was not reported. However, no AEs were reported alongside the use of IDegAsp in these pregnancies.

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 overdose, suicide attempt and use by body builders for an anabolic effect.

Reports of misuse for illegal purposes will be monitored through routine pharmacovigilance. No new safety concerns have been identified from the post-marketing reports concerning misuse or abuse. From the data available, Novo Nordisk does not consider potential for misuse to be a safety concern for IDegAsp.

2.7 Module SVII: Identified and potential risks

2.7.1 Identification of safety concerns in the initial RMP submission

Not applicable as the initial RMP was approved prior to revision 2 of the guideline on good pharmacovigilance practices (GVP) module V coming into effect on the 31 Mar 2017.

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

2.7.2.1 Newly identified safety concerns

No new safety concerns have been identified for IDegAsp.

2.7.2.2 Reclassification of safety concerns

Important identified risks

Hypoglycaemia

Novo Nordisk proposes to remove 'Hypoglycaemia' as an important identified risk in the RMP for IDegAsp. This is in accordance with GVP Module V guidance on RMPs, which states that risks that are fully characterised and managed appropriately may be removed from the safety specification. Hypoglycaemia is a fully characterised and managed risk (see below for details). Specific clinical measures to address hypoglycaemia are fully integrated into clinical practice, and are known to both patients and healthcare professionals. Hypoglycaemia is still considered important identified risks relevant to the benefit-risk profile of IDegAsp and as such is monitored by routine pharmacovigilance and will be reported in the periodic safety update report (PSUR) and development safety update report (DSUR).

Background

As for other insulin products, hypoglycaemia is the most common undesirable reaction for IDegAsp. Hypoglycaemia may occur if the insulin dose is higher than the insulin requirement.

Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Clinical trial data

Table 2-14 shows the confirmed hypoglycaemia rates from IDegAsp clinical trials and Table 2-15 shows the hypoglycaemia rates from the DEVOTE trial. The rates are presented as an estimated rate ratio (IDegAsp/Comparators) with a 95% confidence interval.

Overall, the estimated rate ratios of confirmed hypoglycaemia were lower/comparable in subjects treated with IDegAsp compared to comparators.

Table 2-14 Estimated rate ratios of hypoglycaemia rates from IDegAsp clinical trials

Indication	Dosing regimen	Trial no.	Confirmed	Severe	Nocturnal
T1DM adults	OD	NN5401-3594-3645	0.95 [0.79; 1.14]	0.98 [0.54; 1.79]	0.62* [0.48; 0.79]
T2DM adults	OD	NN5401-3896	0.73 [0.50; 1.08]	Not applicable	0.75 [0.34; 1.64]
		NN5401-3593	1.43* [1.07; 1.92]	Not applicable	0.80 [0.49; 1.30]
		NN5401-3590-3726	1.86* [1.42; 2.44]	Not applicable	0.25* [0.14; 0.47]
	BID	NN5401-3592/ NN5401-3597**	0.81* [0.67; 0.98]	Not applicable	0.43* [0.31; 0.59]
		NN5401-3598	0.57 [0.42; 0.77]	Not applicable	0.53 [0.33; 0.87]
		NN5401-4243	0.26 [0.16; 0.44]	0.56 [0.07; 4.36]	0.17 [0.08; 0.38]
Paediatric T1DM	OD	NN5401-3816	0.95 [0.76; 1.17]	3.20 [0.88; 11.66]	1.09 [0.81, 1.48]

*Statistically significant

**Pooled analysis of hypoglycaemic episodes reported in trials NN5401-3592 and NN5401-3597.

The number of episodes is analysed using a Negative Binomial Regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model includes treatment, sex, region, antidiabetic treatment at screening and trial as fixed effects and age as covariate.

Confirmed hypoglycaemia: subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56mg/dL)

In trial NN5401-4243 statistical analysis was carried out on severe or blood glucose confirmed symptomatic hypoglycaemia events.

Nocturnal period: the period between 00:01 and 05:59 a.m. (both included).

For NN5401-3896, region is not included in the model.

For NN5401-3594-3645 IDet is the comparator.

For NN5401-3896, NN5401-3593, NN5401-3590-3726 IGlar is the comparator.

For NN5401-3592, NN5401-3597, NN5401-4243, NN5401-3598 BIAsp is the comparator.

For NN5401-3816 IDet is the comparator

Abbreviations: BID = twice per day; IDet = insulin detemir; IGlar = insulin glargine; BIAsp = biphasic insulin aspart; OD = once daily; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Table 2-15 Statistical analysis of EAC-number of confirmed severe hypoglycaemic episodes in trial EX1250-4080 (DEVOTE) – T2DM subjects

Indication	Dosing regimen	Trial no.	Confirmed	Severe	Nocturnal
T2DM adults with high risk of CV events	OD	EX1250-4080	N/A	0.60 [0.476; 0.759]	0.47* [0.31; 0.73]

*Statistically significant
Severe hypoglycaemic episodes in the trial were defined according to ADA's definition; an episode of severe hypoglycaemia is an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions.
Nocturnal EAC-confirmed severe hypoglycaemic episodes were defined as EAC-confirmed severe hypoglycaemic episodes with time of onset between 00:01 and 05.59 a.m., both inclusive, as reported by the investigator.
Abbreviations: CV = cardiovascular; EAC = event adjudication committee; T2DM = type 2 diabetes mellitus; OD = once daily.

Post-marketing data

Table 2-16 shows the frequency of hypoglycaemia from post-marketing sources for IDegAsp which is lower than is seen in the general incidence rates observed in the background population.

Table 2-16 Cumulative post-marketing events of hypoglycaemia for IDegAsp

Post-marketing events	Number of events
Total	**164**
Serious	36
Non-serious	128
Exposure in PYE	159,386
Reporting rate of events (events/PYE × 100)	0.10

Note: All of these events were reported in adults. Limited information is available on the severity of these events.
Abbreviations: IDegAsp = insulin degludec/insulin aspart; PYE = patient-years of exposure.

Back ground incidence rates:

- T1DM any/mild/moderate: 15–137 episodes per patient-years [49-56]
- T1DM severe: 0.1–4.9 episodes per patient-years[49-55, 57, 58]
- T2DM any/mild/moderate: 0.2–38.9 episodes per patient-years[53, 54, 59-63]
- T2DM severe: 0–2.5 episodes per patient-years[53, 54, 59-61, 64]

Paediatric population

The frequency of severe hypoglycaemia reported in trial NN1250-3561 should not be directly compared to epidemiological studies as different definitions of severe hypoglycaemia were used in this trial. The prevalence of severe hypoglycaemic events in patients with T1DM showed that one or more events within 12 months occurred in 6.2% of participants (aged 2 to <26 years). Severe hypoglycaemia was more common in participants aged 2 to <6 years than in the older age groups: 9.6% (2 to <6 years), 5.2% (6 to <13 years) and 6.3% (13 to <18 years).[65] In a Danish registry of childhood diabetes, 26% of participants experienced at least one severe hypoglycaemia event over an observation period of 5.9 years (age <15 years).[66]

To minimise the probability and severity of the occurrence of hypoglycaemia with IDegAsp, routine risk minimisation measures have been included in the current Summary of Product Characteristics (SmPC), package leaflets (PLs) and instructions for use (IFU). Of note, it is stated in the SMPC that IDegAsp should be used with special caution in children aged 2 to 5 years old. This is due to data from trial NN5401-3816 indicated that there may be a higher risk for severe hypoglycaemia in children in this age group.

Conclusion

Given the reporting rates from clinical trials are comparable/lower than comparators and that post-marketing reports are stable and lower than is seen in the background population, Novo Nordisk concludes that the risk minimisation measures are adequate and that hypoglycaemia can be removed from the RMP.

Immunological events – Allergic reactions

Novo Nordisk proposes to remove 'Immunological events – Allergic reactions' as an important identified risk in the RMP for IDegAsp. This is in accordance with GVP Module V guidance on RMPs, which states that risks that are fully characterised and managed appropriately may be removed from the safety specification. Immunological events – allergic reactions is a fully characterised and managed risk (see below for details). Specific clinical measures to address allergic reactions are fully integrated into clinical practice, and are known to both patients and healthcare professionals. Immunological events – Allergic reactions is still considered an important identified risk relevant to the benefit–risk profile of IDegAsp and as such is monitored by routine pharmacovigilance and will be reported in the PSUR and DSUR.

Background

Any substance that is not usually found in the human body may serve as an antigen. Therefore, treatment with any protein such as insulin has the propensity to induce an allergic reaction, which can range in severity from mild to severe. Repeated exposure to an allergen may lead to generalised hypersensitivity and more serious reactions can occur including anaphylaxis which is life threatening.

Prevalence

The overall prevalence of allergic reactions to insulin products has been reported in the range from 0.1% to 3,[67, 68] and less than one-third of these events have been considered related to insulin itself.[69, 70] Other reactions occur due to the preservatives added to insulin.[67, 69] Many case reports have been reported in the literature,[71, 72] but the frequency of specific insulin allergic reactions is largely unknown.[67, 69] It should be noted that positive prick test results and low specific IgE titres may occur in up to 28% of diabetes patients without any clinical relevance.[73]

To minimise the probability and severity of the occurrence of allergic reactions with IDegAsp, routine risk minimisation measures have been included in the current Summary of Product Characteristics (SmPC), package leaflets (PLs) and instructions for use (IFU). Hypersensitivity to the active substances or to any of the excipients is a contraindication for the use of IDegAsp.

The frequency of potential allergic reactions in subjects treated in clinical trials with IDegAsp was low (0.1%), which is comparable to the comparators (0.1%) and the background prevalence. No cases of a potential allergic reaction to IDegAsp or comparators were identified in the paediatric trial (NN5401-3816), based on case-by-case analysis. The reporting rates of allergic reactions to IDegAsp from post-marketing sources is also lower than seen in the clinical trials and that is reported in the general population see Table 2-17.

Table 2-17 Number of allergic reaction events reported from post-marketing sources

Post-marketing events	Number of events
Total	**38**
Serious	3
Non-serious	35
Exposure in PYE	159,386
Reporting rate of events (events/PYE × 100)	0.002

None of these events were associated with fatal outcome. Limited information is available on the severity of the events reported from post-marketing data sources.

Conclusion

Given the reporting rates from clinical trials are comparable/lower than comparators and that post-marketing reports are stable and lower than is seen in the background population. Novo Nordisk concludes that the risk minimisation measures are adequate and that 'Immunological events – allergic reactions' can be removed from the RMP.

Missing information

According to the updated GVP module V revision 2, populations that are not within the approved indication should not be considered as missing information. Accordingly, as IDegAsp is not

indicated in the 3 following populations, Novo Nordisk proposes to remove them as missing information:

- Children under 1 year of age
- Co-administration with a glucagon-like peptide-1 (GLP-1) analogue
- Pregnancy

Elderly patients aged ≥75 years with T1DM

Elderly patients aged ≥75 years with T1DM was previously classified as missing information as exposure to IDegAsp and IDeg was limited in subjects with T1DM aged ≥75 years in the main clinical trial programmes. Novo Nordisk proposes to remove this category as missing information.

The clinical trial programmes of IDegAsp and IDeg contained more than 4,000 older adults (≥65 and ≥75 years) with T2DM (see Table 2-8 and Table 2-7). Whereas, 21 subjects with T1DM who were aged over 75 years were exposed to IDeg/IDegAsp. The frequency, type and severity of adverse events observed in the older adults were not different from that of the younger adult population. Trial NN1250-3995 included 46 exposed subjects aged ≥65 years, 10 of these were subjects aged ≥75 years. Mean HbA_{1c} levels and the proportion of subjects reporting serious adverse events (SAEs) were similar between the elderly (≥65 years) and younger adult population. The proportion of subjects reporting severe or blood glucose-confirmed symptomatic hypoglycaemic episodes with IDeg treatment were numerically lower in the elderly compared to the younger adult population in this trial. No new safety concerns were identified with advancing age and IDeg treatment.

No special precautions are needed in this population and therefore the use of IDegAsp in elderly patients (≥75 years) with T1DM is no longer considered missing information. In addition, safety data from this population are being evaluated in post-marketing surveillance and there are no indications that this population has a safety profile different from the general population.

Patients with hepatic impairment

Subjects with severe hepatic impairment were excluded from most of the clinical development programmes; however, a clinical pharmacology trial (NN1250-1989) investigated the safety and pharmacokinetic (PK) properties of IDeg in subjects with normal or impaired (mild, moderate or severe) hepatic function following administration of a single dose (0.4 units/kg) of IDeg. The PK properties of IDeg after a single dose were similar in subjects with or without hepatic impairment. There was no indication of a difference in the AE pattern between the treatment groups.

A total of 40 subjects with mild to moderate hepatic impairment (classified according to the Child–Pugh classification) have been exposed to IDegAsp/IDeg in all completed clinical trials. Furthermore, trial EX1250-4080 (DEVOTE) included a total of 102 randomised subjects with hepatic impairment at baseline. The overall distribution of SAEs reported from subjects with

hepatic impairment was similar between the two treatment arms (IDeg and IGlar) and therefore did not give rise to any new safety concerns.

Based on the exposure of IDeg/IDegAsp in patients with hepatic impairment, Novo Nordisk concludes that the safety profile in this population does not differ from the safety profile characterised so far. Therefore, Novo Nordisk proposes to remove this population as missing information**.**

Patients with renal impairment

Patients with renal impairment was previously classified as missing information. Novo Nordisk proposes to remove this category as missing information. A total of 983 subjects with mild to moderate renal impairment have been exposed to IDegAsp throughout the clinical trial programme. A further 3,025 subjects with renal impairment were exposed to IDeg in the CVOT EX1250-4080 (DEVOTE). Of the 3,025 subjects exposed in the DEVOTE trial, 108 of these subjects had severe renal impairment. Change in renal function from baseline to the last assessment was a secondary safety endpoint for the trial. No clinically relevant differences between treatment groups were noted. There was no difference in the frequency, type or severity of the adverse events reported in subjects with renal impairment compared to subjects without renal impairment.

Based on the exposure of IDeg/IDegAsp in patients with renal impairment, Novo Nordisk concludes that the safety profile in this population does not differ from the safety profile characterised so far. Therefore, Novo Nordisk proposes to remove this population as missing information.

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

2.7.3.1 Important identified risk

There are no important identified risks for the RMP of IDegAsp.

2.7.3.2 Important potential risk: Medication errors due to mix-up between IDegAsp and bolus insulin

Potential mechanisms

Medication errors may occur for a number of reasons; examples include; lack of training before initiating insulin therapy, a patient's unawareness of difference between basal and bolus insulin, distraction during preparation for injection, etc.

Evidence source and strength of evidence

Completed therapeutic confirmatory trials using the marketed device (phase 3a and 3b trials) in which IDegAsp was used as the investigational drug and market experience up until the DLP of this report are the evidence sources of this risk. Medication errors in clinical trials are systematically collected and the cases are well documented. However, clinical trials are unrepresentative of clinical practice. Post-marketing data in this table include events from all spontaneous cases (including literature cases), non-interventional studies and other solicited sources. There have been very few spontaneous reports of mix-up between IDegAsp and bolus insulin reported in both clinical trials and from post-marketing cases. Therefore, an association between mix-ups between IDegAsp and bolus insulins remains plausible but weak.

Characterisation of the risk:

Table 2-18 Overview of all treatment-emergent medication errors – Mix-ups between basal and bolus in confirmatory trials - IDegAsp - Non-paediatric, T1DM+ T2DM – Safety analysis set

	IDegAsp				IDeg				Other comparator			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
All subjects	382				20				180			
Exposure (years)	306				9				145			
All events	9	(2.4)	10	3.3	1	(5.0)	1	11.4	6	(3.3)	6	4.1
Serious	1	(0.3)	1	0.3								
Non-serious	8	(2.1)	9	2.9	1	(5.0)	1	11.4	6	(3.3)	6	4.1
Severe									1	(0.6)	1	0.7
Moderate	6	(1.6)	6	2.0					3	(1.7)	3	2.1
Mild	3	(0.8)	4	1.3	1	(5.0)	1	11.4	2	(1.1)	2	1.4
Unknown												
Relation to trial product												
Possibly/probably	2	(0.5)	2	0.7					1	(0.6)	1	0.7
Unlikely	7	(1.8)	8	2.6	1	(5.0)	1	11.4	5	(2.8)	5	3.4
Unknown												
Outcome												
Fatal												
Recovered	9	(2.4)	10	3.3	1	(5.0)	1	11.4	6	(3.3)	6	4.1
Recovering												
Recovered with sequelae												
Not recovered												
Unknown												

Cumulative reporting period to 31-Jan-2018
N: Number of subjects; %: Percentage of subjects; E: Number of events; R: Events/100 Exposure Years;
MedDRA Version [20.1];
Relationship to trial drug is based on investigator(s)'s assessment.
Table only includes treatment emergent adverse events defined as adverse events occurring between first day on trial product until last day on trial product + [7 days].
Trials included:
NN5401-3594-3645, NN5401-4003
Other comparator: IDet

Table 2-19 Overview of all treatment-emergent medication errors – Mix-ups between basal and bolus in confirmatory trials – IDegAsp – Paediatric, T1DM – Safety analysis set

	IDegAsp				Comparator			
	N	(%)	E	R	N	(%)	E	R
All subjects	181				179			
Exposure (years)	55				54			
All events	4	(2.2)	4	7.3	2	(1.1)	2	3.7
Serious								
Non-serious	4	(2.2)	4	7.3	2	(1.1)	2	3.7
Severe								
Moderate	2	(1.1)	2	3.7				
Mild	2	(1.1)	2	3.7	2	(1.1)	2	3.7
Unknown								
Relation to trial product								
Possibly/probably	1	(0.6)	1	1.8				
Unlikely	3	(1.7)	3	5.5	2	(1.1)	2	3.7
Unknown								
Outcome								
Fatal								
Recovered	4	(2.2)	4	7.3	2	(1.1)	2	3.7
Recovering								
Recovered with sequelae								
Not recovered								
Unknown								
Events leading to discontinuation of randomised treatment								

Cumulative reporting period to 31-Jan-2018
N: Number of subjects; %: Percentage of subjects; E: Number of events; R: Events/100 Exposure Years;
MedDRA Version [20.1];
Relationship to trial drug is based on investigator(s)'s assessment.
Table only includes treatment emergent adverse events defined as adverse events occurring between first day on trial product until last day on trial product + [7 days].
Trials included:
NN5401-3816
Comparator: IDet

Table 2-20 Number of events concerning mix-ups from post-marketing sources

Post-marketing events	Number of events
Total	**4**
Serious	1
Non-serious	3
Exposure in PYE	168,893
Reporting rate of events (events/PYE × 100)	0.002

Note: The post-marketing cases concerning mix ups between IDegAsp and bolus insulin are assessed on a case by case basis.

Abbreviations: PYE = patient-years of exposure.

The background incidence rate for medication errors – mix up between basal and bolus insulin is unknown. Data on prevalence are also limited. The prevalence of packaging mix-ups of insulin products, infusion fluids and prepared syringes when self-injecting is expected to be of the same magnitude as the error rate for healthcare professionals (around 7%).[74] However, these data cannot be used to draw comparisons as IDegAsp is administered using a prefilled pen.

Therefore, the rates of medication errors of mix-ups between IDegAsp and bolus insulin in clinical trials and from post-marketing sources appear to be lower than the prevalence reported for injecting insulins with syringes in the literature.

Risk factors and risk groups

All diabetes patients on a regimen of IDegAsp plus bolus insulin plus patients with a spouse who has diabetes are at risk of mix-ups between IDegAsp and bolus insulin. Visually impaired or colour-blind patients may be at higher risk.

Preventability

Mix-ups between IDegAsp and bolus insulin is a risk that can theoretically be prevented as it is generally caused by human error. The main activity to minimise this risk is the product differentiation strategy. This includes trade names, label text, colour branding of the carton, container label and cartridge holder. To avoid accidental mix-ups, patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between IDegAsp and other insulin products.

Impact on the benefit-risk balance of the product

Mix-ups between IDegAsp and bolus insulin could have serious consequences, potentially including death. However, taking the current risk minimisation measures into consideration Novo Nordisk considers the impact of mix-ups between IDegAsp and bolus insulin on the benefit–risk profile of IDegAsp to be low.

Public health impact

The overall public health impact is evaluated as low. There are very few post-marketing events reported, and 100% of those reported are non-serious. It is therefore concluded that the public health impact is sufficiently minimised by the routine risk minimisation measures in place for IDegAsp.

2.7.3.3 Important potential risk: Immunological events – formation of insulin neutralising antibodies

Potential mechanisms

Any substance that is not usually found in the human body may serve as an antigen. Therefore, treatment with any protein has the propensity to induce antibody formation. Formulation of insulin neutralising antibodies is a potential risk of all insulins. The main clinical observation associated with neutralising antibodies is lack of efficacy.

Evidence source and strength of evidence

All completed clinical trials in which IDegAsp was used as investigational drug and market experience until the DLP of this report are the evidence sources for the evaluation of this risk. Post-marketing data include events from all spontaneous cases (including literature cases), non-interventional studies and other solicited sources. The formation of antibodies in response to human and analogue insulins is a well-established phenomenon. However, observational data on antibody development in response to IDegAsp or IDeg are lacking. Very few cases have been reported in clinical trials and in post-marketing reports. Furthermore, no clinical manifestation was observed in reported cases. Therefore, the strength of evidence for formulation of insulin neutralising antibodies in response to IDegAsp is plausible but weak.

Characterisation of the risk:

There have been no cases of formation of IDegAsp neutralising antibodies in the clinical trial programme.

Overview of events from post-marketing sources

No cases have been reported with neutralising anti-insulin antibodies for IDegAsp up until the DLP of this report. Three (3) cases were reported with ‘anti-insulin antibody positive’ and co-reported hyperglycaemia. A Review of these cases did not identify reasons for new safety concerns.

Risk factors and risk groups

All diabetes patients on a regimen of IDegAsp.

Preventability

There are currently no preventative measures for this risk. If the risk is identified as a safety issue, and a lack of efficacy is observed the labelling will be updated accordingly.

Impact on the benefit–risk balance of the product

In rare cases, neutralising antibodies may negatively affect the efficacy or safety in a subgroup of patients. No reports of neutralising antibodies were reported in clinical trials with IDegAsp. Novo Nordisk evaluates that the potential of IDegAsp-neutralising insulin antibody development has a very low impact on the benefit–risk balance. This is because the immunogenic response when observed did not result in any safety issues. However, if IDegAsp neutralising antibodies are detected treatment with the product should be stopped. .

Public health impact

The public health impact of this potential risk is considered low. In rare cases, neutralising antibodies may negatively affect the efficacy or safety in a subgroup of patients. However, no reports of neutralising antibodies were reported in clinical trials and very few in post-marketing data following dosing of IDegAsp. If a causal relationship is observed between IDegAsp administration and insulin neutralising antibodies, the frequency is expected to be so low that it will not impact on public health.

2.7.3.4 Missing information:

There is no missing information for IDegAsp.

2.8 Module SVIII: Summary of safety concerns

Table 2-21 Summary of safety concerns – IDegAsp

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Medication due to mix-up between IDegAsp and bolus insulin • Immunological events – formation of insulin neutralising antibodies
Missing information	None

Abbreviations: IDegAsp = insulin degludec/insulin aspart.

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 health care professional will be made to ascertain the missing information. There is a standard form of information required to maximise the evaluation of the data across all of Novo Nordisk's insulins. The current medication error form is attached in Annex 4. This form is expected to develop over time in response to feedback from health authorities and health care professionals.

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 IDegAsp.

3.3 Summary table of additional pharmacovigilance activities

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

4 Plans for post-authorisation efficacy studies

There are currently no plans for post-authorisation efficacy studies for IDegAsp

5 Risk minimisation measures

5.1 Routine risk minimisation measures

5.1.1 Important potential risks

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

Safety concern	Routine risk minimisation measures
Immunological events – Formulation of neutralising insulin antibodies	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Addressed in SmPC section 4.4 where advice is given stating that if insulin neutralising antibodies are detected the insulin dose may require adjusting.

Safety concern	Routine risk minimisation measures
	Other risk minimisation measures beyond the Product Information: None proposed
Medication error – mix-up between IDegAsp and bolus insulin	**Routine risk communication:** Product differentiation strategy including: trade names, label text, colour branding of the carton, container label and cartridge holder. **Text in SmPC** Section 4.4 Avoidance of accidental mix-ups. Advice on practical actions to minimise the risk is given, for example for patients to check the insulin label before each injection and that a syringe should never be used to draw the medicinal product from the cartridge of a pre-filled pen. Section 6.6: Special precautions for disposal and other handling Patient leaflet: • Instructions on how to inject IDegAsp are provided. • Specific information on how to use IDegAsp by patients who are blind or have poor eyesight and cannot read the dose counter on the pen. Other risk minimisation measures beyond the Product Information: Follow-up procedure to improve the quality of the medication error reports.

Abbreviations: IDegAsp = insulin degludec/insulin aspart; SmPC = Summary of Product Characteristics.

5.1.2 Missing information

This section is not applicable as there is no missing information for IDegAsp.

5.2 Additional risk minimisation measures

Routine risk minimisation activities as described in Section 5.1 are sufficient to manage the safety concerns of the medicinal product.

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

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Medication error – mix-up between IDegAsp and bolus insulin	• Product differentiation strategy including: trade names, label text, colour branding of the carton, container label and cartridge holder. Text in SmPC • Section 4.4 Avoidance of accidental mix-ups • Section 6.6: Special precautions for disposal and other handling	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for adverse reaction
Immunological events – formation of insulin neutralising antibodies	Routine risk minimisation measures: • Addressed in SmPC section 4.4 where advice is given on insulin antibodies Additional risk minimisation measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None

Abbreviations: AE = adverse event; SmPC = Summary of Product Characteristics.

6 Summary of the risk management plan for Ryzodeg® (Insulin degludec/insulin aspart)

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

Ryzodeg®'s summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Ryzodeg® should be used.

This summary of the RMP for Ryzodeg® 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 Ryzodeg®'s RMP.

6.1 The medicine and what it is used for

Ryzodeg® is authorised for the treatment of diabetes mellitus (see SmPC for the full indication). It contains insulin degludec and insulin aspart as the active substances and it is given by subcutaneous injection.

Further information about the evaluation of Ryzodeg®'s benefits can be found in Ryzodeg®'s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: link

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

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

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

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

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

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

6.2.1 List of important risks and missing information

Important risks of Ryzodeg® 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 Ryzodeg®. 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 between IDegAsp and bolus insulin • Immunological events – formulation of insulin neutralising antibodies
Missing information	None

Abbreviations: IDegAsp = insulin degludec/insulin aspart.

6.2.2 Summary of important risks

6.2.2.1 Important identified risks

None.

6.2.2.2 Important potential risks

Table 6-2 Medication error – Mix-up between IDegAsp and bolus insulin

Evidence for linking the risk to the medicine	Completed therapeutic confirmatory trials using the marketed device (phase 3a and 3b trials) in which IDegAsp was used as the investigational drug and market experience up until the DLP of this report are the evidence sources of this risk. Medication errors in clinical trials are systematically collected and the cases are well documented. However, clinical trials are unrepresentative of clinical practice. Post-marketing data include events from all spontaneous cases (including literature cases), non-interventional studies and other solicited sources. There have been very few spontaneous reports of mix-up between IDegAsp and bolus insulin reported in both clinical trials and from post- marketing cases. Therefore, an association between mix-ups between IDegAsp and bolus insulins remains plausible but weak.
Risk factors and risk groups	All diabetes patients on a regimen of IDegAsp plus bolus insulin plus patients with a spouse who has diabetes are at risk of mix-ups between IDegAsp and bolus insulin. Visually impaired or colour-blind patients may be at higher risk.
Risk minimisation measures	**Routine risk minimisation measures** Product differentiation strategy including: trade names, label text, colour branding of the carton, container label and cartridge holder. **Text in SmPC** Section 4.4 Avoidance of accidental mix-ups Section 6.6: Special precautions for disposal and other handling Additional risk minimisation measures *None*

Abbreviations: DLP = data lock point; IDegAsp = insulin degludec/insulin aspart; SmPC = Summary of Product Characteristics.

Table 6-3 Immunological events – Formation of insulin neutralising antibodies

Evidence for linking the risk to the medicine	All completed clinical trials in which IDegAsp was used as investigational drug and market experience until the DLP of this report are the evidence sources for the evaluation of this risk. Post-marketing data include events from all spontaneous cases (including literature cases), non-interventional studies and other solicited sources. The formation of antibodies in response to human and analogue insulins is a well-established phenomenon. However, observational data on antibody development in response to IDegAsp or IDeg are lacking. Very few cases have been reported in clinical trials and in post-marketing reports. Furthermore, no clinical manifestation was observed in reported cases. Therefore, the strength of evidence for formulation of insulin neutralising antibodies in response to IDegAsp is plausible but weak.
Risk factors and risk groups	All diabetes patients on an insulin regime
Risk minimisation measures	**Routine risk minimisation measures:** Addressed in SmPC section 4.4 where advice is given on insulin antibodies **Additional risk minimisation measures:** None

Abbreviations: DLP = data lock point; IDegAsp = insulin degludec/insulin aspart; 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 obligations for IDegAsp.

6.2.3.2 Other studies in post-authorisation development plan

There are no studies required for IDegAsp.

Risk Management Plan

IDegAsp

Annex 4 - Specific adverse event follow-up forms

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Please type or use capital letters

Novo Nordisk

Medication Error Form

Patient Identification: Initials/ID……. Age/Date of birth…….. Sex/Gender ☐ F ☐ M

Background information

Has the patient recently switched from another product (within last 3 months)?	☐ Yes ☐ No
Is this the first time that the patient is treated for this indication?	☐ Yes ☐ No
Did the patient experience the same Medication Error in the past?	☐ Yes ☐ No
Was the product received in the original packaging? If no, please specify: _____	☐ Yes ☐ No

Persons involved – e.g. staff or health care professional who made an error

☐ Physician	☐ Nurse	☐ Other (specify)_____
☐ Pharmacist	☐ Patient/caregiver	☐ Unknown

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 (specify)_____

Why do you think the Medication Error occurred

☐ Miscalculation of dose ☐ Products look alike ☐ Wrong instructions for product use ☐ Distraction
☐ Drug names alike ☐ Insufficient lighting ☐ Poor eye sight/colour blindness ☐ Insufficient training
☐ Misunderstanding of product label information (if ticked please specify below)
☐ Other (specify)_____

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

Description of any Adverse Events (AEs) that have occurred as a consequence of the medication error

Did the patient experience any AEs as a consequence of the Medication Error? ☐ Yes ☐ No If yes, specify:_____	Onset date of the AE associated with Medication Error d d m m y y y y	Stop date of the AE associated with Medication Error d d m m y y y y

Any treatment of the AE associated with the Medication Error? ☐ Yes ☐ No
If yes, please specify: _____

Product(s) returned to Novo Nordisk for investigation ☐ Yes ☐ No

Date: Reporter's signature:

NN internal use only

NN Receipt date d d m m y y y y | By Initials | First NN employee GS date and initials. | Global Safety GS Case No.

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Risk Management Plan

IDegAsp

Annex 6 - Details of proposed additional risk minimisation measures

This Annex is not applicable for this version of the Risk Management Plan