Risk Management Plan

Insulin aspart

Active substance(s)	Insulin aspart
RMP version number	3.1
Data lock point for this RMP	31 Jan 2018
Date of final sign off	See signature page
Rationale for submitting an updated RMP	Submission in connection with variation application titled '*NovoMix® 30 combination use with GLP-1 receptor agonists*'
Summary of significant changes in this RMP	The RMP has been updated using the new template based on the requirements in GVP Module V – Risk management systems (Rev.2). Significant changes have been made to the safety specification as several risks are considered fully characterised and appropriately managed and therefore do not need further risk management. Missing information in different age groups and populations has been removed. The RMP has also been updated according to the approved extension of the paediatric indication to include children from the age of 1 year, and clinical trial exposure data from the Victoza® LEADER trial (trial EX2211-3748) in order to support the label update for NovoMix® 30 combination use with GLP-1 receptor agonists.
Other RMP versions under evaluation	None
Details of the currently approved RMP	Version number: Edition 2, Version 1 Approved with procedure: EMEA/H/C/258/II/0111 Date of approval (opinion date): 23 Jun 2016
QPPV Delegate	[redacted]
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RIMS change ID: 18032

Abbreviations

ADA	American Diabetes Association
ADR	adverse drug reaction
AE	adverse event
CFDA	Chinese Food and Drug Administration
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CSII	continuous subcutaneous insulin infusion
DLP	data lock point
DM	diabetes mellitus
DPP-4	dipeptidyl peptidase-4
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
EPAR	European public assessment report
ESRD	end-stage renal disease
GLP-1	glucagon-like peptide-1
GVP	Guideline on good pharmacovigilance practices
HbA1c	glycosylated haemoglobin
HCP	healthcare professional
HDL	high-density lipoprotein
HIE	high-dose insulin/euglycaemia
HR	hazard ratio
IDF	International Diabetes Federation
IFG	impaired fasting glucose
IFU	instructions for use
IGT	impaired glucose tolerance
IMP	investigational medicinal product
LEADER	Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results
MAH	marketing authorisation holder
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NCD	non-communicable disease
NPH	neutral protamine Hagedorn
NYHA	New York Heart Association
OAD	oral antidiabetic drug
PBRER	periodic benefit–risk evaluation report
PIL	patient information leaflet
PL	package leaflet
PSUR	periodic safety update report
PYE	patient-years of exposure
RMP	risk management plan
RR	reporting rate
SDEA	Safety Data Exchange Arrangement
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA query
T1DM	type 1 diabetes mellitus

T2DM	type 2 diabetes mellitus
TIA	transient ischaemic attack
WHO	World Health Organization

1 Products overview

This risk management plan (RMP) concerns 4 formulations of insulin aspart: soluble insulin aspart formulation (NovoRapid®) and 3 biphasic formulations where protamine is added in different percentages (NovoMix® 30, NovoMix® 50 and NovoMix® 70).

The product details for the above-mentioned insulin aspart products are shown in Table 1-1 (NovoRapid®) and Table 1-2 (NovoMix®).

Table 1-1 Product overview, NovoRapid®

Active substance(s) (INN or common name)	Insulin aspart
Pharmacotherapeutic group(s) (ATC Code)	A10AB05
Marketing authorisation holder/applicant	EU: Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark
Medicinal products to which this RMP refers	NovoRapid® and NovoMix® (NovoMix® 30/50/70 [Table 1-2])
Invented name(s) in the European Economic Area (EEA)	• NovoRapid® 100 units/mL solution for injection in vial • NovoRapid® Penfill® 100 units/mL solution for injection in cartridge • NovoRapid® FlexPen® 100 units/mL solution for injection in prefilled pen • NovoRapid® InnoLet® 100 units/mL solution for injection in prefilled pen • NovoRapid® FlexTouch® 100 units/mL solution for injection in prefilled pen • NovoRapid® PumpCart® 100 units/mL solution for injection in cartridge
Marketing authorisation procedure	Centralised
Brief description of the product	Rapid-acting insulin analogue ***Pharmaco-therapeutic group:*** Drugs used in diabetes. Insulins and analogues for injection, fast-acting; A10AB05 ***Structural formula:*** In insulin aspart (molecular formula $C_{256}H_{381}N_{65}O_{79}S_6$), proline has been substituted by aspartic acid in position B28 in the insulin molecule. The insulin comes from the fermentation of genetically modified yeast cells (rDNA origin, *Saccharomyces cerevisiae*).
	Mode of action: The aspartic acid at position 28 in the B-chain of insulin aspart produces intermolecular charge repulsion, thereby reducing the tendency of the insulin molecules to self-associate and form hexamers in vials and cartridges.
	Composition: 1 mL of the solution contains 100 units of insulin aspart equivalent to 3.5 mg.

Hyperlink to the Product Information:	NovoRapid® PI
Indication(s) in the EEA	**Current:** Treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.
	Proposed: Not applicable
Dosage in the EEA	**Current:** Dosing of NovoRapid® is individualised and determined in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin. The individual insulin requirement in adults and children is usually between 0.5 and 1.0 units/kg/day. In a basal–bolus treatment regimen, 50–70% of this requirement may be provided by NovoRapid® and the remainder by intermediate-acting or long-acting insulin.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** NovoRapid® is available as a 100 units/mL solution for injection in 10 mL vial, 3 mL Penfill®, 3 mL InnoLet®, 3 mL FlexPen® and 3 mL FlexTouch®. The 3 mL Penfill® is for use with Novo Nordisk durable insulin-delivery devices. The InnoLet®, FlexPen® and FlexTouch® products are prefilled disposable pens. NovoRapid® is also available as NovoRapid® PumpCart®, a 1.6 mL 100 units/mL prefilled cartridge designed for CSII in the Accu-Chek® Insight and YpsoPump® insulin pumps.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations: ATC = anatomical therapeutic chemical; CSII = continuous subcutaneous insulin infusion; EEA = European Economic Area; INN = international nonproprietary name; PI = product information.

Table 1-2 Product information, NovoMix®

Active substance(s) (INN or common name)	Insulin aspart
Pharmacotherapeutic group(s) (ATC Code)	A10AD05
Marketing authorisation holder/applicant	EU: Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark
Medicinal products to which this RMP refers	NovoRapid® (Table 1-1) and NovoMix® (NovoMix® 30/50/70)
Invented name(s) in the European Economic Area (EEA)	• NovoMix® 30 Penfill® 100 units/mL suspension for injection in cartridge • NovoMix® 50 Penfill® 100 units/mL suspension for injection in cartridge • NovoMix® 70 Penfill® 100 units/mL suspension for injection in cartridge • NovoMix® 30 FlexPen® 100 units/mL suspension for injection in prefilled pen • NovoMix® 50 FlexPen® 100 units/mL suspension for injection in prefilled pen • NovoMix® 70 FlexPen® 100 units/mL suspension for injection in prefilled pen
Marketing authorisation procedure	Centralised
Brief description of the product	Biphasic insulin aspart ***Pharmaco-therapeutic group:*** Drugs used in diabetes. Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting; A10AD05 ***Structural formula:*** In insulin aspart (molecular formula $C_{256}H_{381}N_{65}O_{79}S_6$), proline has been substituted by aspartic acid in position B28 in the insulin molecule. The insulin comes from the fermentation of genetically modified yeast cells (rDNA origin, *Saccharomyces cerevisiae*). NovoMix® is a sterile biphasic suspension consisting of different ratios of soluble (rapid-acting) insulin aspart and protamine-crystallised (intermediate-acting) insulin aspart. For NovoMix® 30 the ratio is 30/70, for NovoMix® 50 the ratio is 50/50 and for NovoMix® 70 the ratio is 70/30.
	Mode of action: The aspartic acid at position 28 in the B-chain of insulin aspart produces intermolecular charge repulsion, thereby reducing the tendency of the insulin molecules to self-associate and form hexamers in vials and cartridges. In NovoMix® 30, 70% of the insulin aspart is crystallised with protamine to cause delayed absorption properties. In NovoMix® 50 and NovoMix® 70, 50% and 30%, respectively, of the insulin aspart is crystallised with protamine. The time action profile of the protamine-crystallised insulin aspart was similar to NPH insulin in animal studies.
	Composition: 1 mL of the suspension contains 100 units of soluble insulin aspart/protamine-crystallised insulin aspart in the ratio 30/70, 50/50 or 70/30 (equivalent to 3.5 mg insulin aspart, regardless of ratio).

Hyperlink to the Product Information:	NovoMix® PI
Indication(s) in the EEA	**Current:** Treatment of diabetes mellitus in adults. Furthermore, NovoMix® 30 is also indicated for use in adolescents and children aged 10 years and above.
	Proposed: Use of NovoMix® 30 in combination with GLP-1 receptor agonists.
Dosage in the EEA	**Current:** Dosing of NovoMix® is individualised and determined in accordance with the needs of the patient. <u>NovoMix® 30:</u> In patients with T2DM, NovoMix® 30 can be given as monotherapy. NovoMix® 30 can also be given in combination with oral antidiabetic medicinal products if the patient's blood glucose is inadequately controlled with oral antidiabetic medicinal products alone. For patients with T2DM, the recommended starting dose of NovoMix® 30 is 6 units at breakfast and 6 units at dinner (evening meal). NovoMix® 30 can also be initiated once daily with 12 units at dinner (evening meal). When using NovoMix® 30 once daily, it is generally recommended to move to twice daily when reaching 30 units by splitting the dose into equal breakfast and dinner doses. If twice daily dosing with NovoMix® 30 results in recurrent daytime hypoglycaemic episodes, the morning dose can be split into morning and lunchtime doses (thrice-daily dose). In patients with type 1 diabetes, the individual insulin requirement is usually between 0.5 and 1.0 units/kg/day. NovoMix® 30 may fully or partially meet this requirement. <u>NovoMix® 50:</u> The individual insulin requirement is usually between 0.5 and 1.0 units/kg/day in adult patients and this may be fully or partially supplied with NovoMix® 50. In patients with T2DM, NovoMix® 50 can be given as monotherapy or in combination with metformin, when the blood glucose is inadequately controlled with metformin alone. <u>NovoMix® 70:</u> The individual insulin requirement is usually between 0.5 and 1.0 units/kg/day in adult patients and this may be fully or partially supplied with NovoMix® 70. In patients with T2DM, NovoMix® 70 can be given as monotherapy, or in combination with metformin, when the blood glucose is inadequately controlled with metformin alone.
	Proposed: Dosing of NovoMix® is individualised and determined in accordance with the needs of the patient. <u>NovoMix® 30:</u> In patients with T2DM, NovoMix® 30 can be given as monotherapy.

	NovoMix® 30 can also be given in combination with oral antidiabetic medicinal products and/or GLP-1 receptor agonists. For patients with T2DM, the recommended starting dose of NovoMix® 30 is 6 units at breakfast and 6 units at dinner (evening meal). NovoMix® 30 can also be initiated once daily with 12 units at dinner (evening meal). When using NovoMix® 30 once daily, it is generally recommended to move to twice daily when reaching 30 units by splitting the dose into equal breakfast and dinner doses. If twice daily dosing with NovoMix® 30 results in recurrent daytime hypoglycaemic episodes, the morning dose can be split into morning and lunchtime doses (thrice-daily dose). When a GLP-1 receptor agonist is added to NovoMix® 30, a dose reduction of a minimum of 20% is recommended for patients with an HbA_{1c} less than 8% to minimise the risk of hypoglycaemia. For patients with an HbA_{1c} higher than 8%, a dose reduction should be considered. Subsequently, dosage should be adjusted individually. In patients with type 1 diabetes, the individual insulin requirement is usually between 0.5 and 1.0 units/kg/day. NovoMix® 30 may fully or partially meet this requirement. <u>NovoMix® 50:</u> The individual insulin requirement is usually between 0.5 and 1.0 units/kg/day in adult patients and this may be fully or partially supplied with NovoMix® 50. In patients with T2DM, NovoMix® 50 can be given as monotherapy or in combination with metformin, when the blood glucose is inadequately controlled with metformin alone. <u>NovoMix® 70:</u> The individual insulin requirement is usually between 0.5 and 1.0 units/kg/day in adult patients and this may be fully or partially supplied with NovoMix® 70. In patients with T2DM, NovoMix® 70 can be given as monotherapy, or in combination with metformin, when the blood glucose is inadequately controlled with metformin alone.
Pharmaceutical form(s) and strengths	**Current:** NovoMix® 30, 50 and 70 are available as a 100 units/mL suspension for injection in 3 mL Penfill® or 3 mL FlexPen®.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations: ATC = anatomical therapeutic chemical; EEA = European Economic Area; GLP-1 = glucagon-like peptide-1; NPH = neutral protamine Hagedorn; PI = product information; T2DM = type 2 diabetes mellitus.

2 Safety specification

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

2.1.1 Diabetes mellitus

Diabetes mellitus (DM) 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 (T1DM) is characterised by an autoimmune pancreatic β-cell destruction leading to absolute insulin deficiency. People with T1DM need injections of insulin every day to control the levels of glucose in their blood in order to survive.

Type 2 diabetes mellitus (T2DM) is a heterogeneous, chronic, progressive disease characterised by insulin resistance, along with relatively impaired β-cell function. While the course of development of the disease is variable, it usually follows a predictable course of deteriorating β-cell function and increasing insulin resistance.

2.1.1.1 Incidence and prevalence

Incidence

Overall, the incidence of T2DM is greater than that of T1DM.

The incidence of T1DM is increasing in both children and adults; however, there are strong geographical differences. The overall annual increase is estimated to be around 3%.[2] In 2017, the International Diabetes Federation (IDF) estimated that worldwide more than 96,000 children in the age group 0–14 years develop T1DM annually.[2] In Europe, the incidence ranged from 5.4 per 100,000 in Romania (2013)[3] to 62.3 in Finland in 2015.[2] In the US, an incidence rate of 27.4 new cases per 100,000 children (0–20 years of age) has been reported.[4]

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.[5-20] Although incidence of diabetes continues to increase in some countries such as the UK, data from Denmark and the US indicate that the incidence of diabetes has been stabilising over the past years.[21]

Prevalence

In 2017, the estimated prevalence of DM was 425 million, representing 8.8% of the world's adult population (aged 20–79 years).[2] IDF estimated that globally 50% of all patients with DM are undiagnosed.[2] In the IDF region Europe (covering 57 countries and territories), the prevalence of DM in the adult population was 10.2% in 2017. The countries with the highest prevalence rates of DM in the IDF region Europe in 2015 were Malta (13.8%), Portugal (14.9%), Serbia (13.4%) and Germany (13.4%).[2] Taking the effect of age on prevalence into account, countries with the highest

age-adjusted comparative prevalence rates (standardised to the World population) of DM were Turkey (11.9%), Serbia (9.9%), Portugal (9.9%), Montenegro (9.9%), Macedonia (9.9%), Bosnia and Herzegovina (9.9%) and Albania (9.9%).[2]

At the global level, densely populated countries like China, India and the US represent countries with the largest absolute numbers of patients with T2DM in 2017; this is projected to continue until 2045.[2] The relative proportions of T1DM and T2DM have not been studied in great detail in low- and middle-income countries.[22] In high-income countries, approximately 87–91% of all patients with DM are estimated to have T2DM, 7–12% are estimated to have T1DM and 1–3% to have other types of DM. About 75% of all adults with DM live in low- and middle-income countries.[22]

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

T1DM

T1DM is the predominant type of DM in childhood and adolescence, accounting for >90% of all DM cases in white youth aged <20 years.[8, 23] In most populations, T1DM 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]; however, clinical presentation of T1DM may occur at any age.[8] Approximately one quarter of patients with T1DM are diagnosed as adults.[29]

Although many autoimmune diseases disproportionately affect women, girls and boys are equally affected by T1DM in paediatric cases.[29, 30] Studies on incidence of T1DM have shown no gender differences in the 0–14-year-old patients, and higher incidence among males than females older than 15 years.[8, 31] In contrast to children, there is a consistent male excess of T1DM in populations of European origin aged 15–39 years (female:male ratio ~1:5).[32]

Populations of European origin are subject to both the highest incidence and the highest prevalence of T1DM globally.[22]

T2DM

T2DM usually occurs in adults, but is increasingly seen in children and adolescents. Age is one of the important, yet unmodifiable, risk factors for T2DM, and the prevalence of T2DM becomes progressively higher with advancing age.[22] Not only does diabetes *prevalence* increase with age, a UK retrospective population-based study based on data from *the Clinical Practice Research Datalink (CPRD)* reported a similar tendency of increase in *incidence rates* of T2DM with increasing age group. For the most recent study period, 2006–2010, the incidence rate for T2DM increased with advancing age until 79 years of age and peaked at ages 70–79 years (in both genders).[10] In *the IDF* Region Europe, 30.8% of the general population are aged between 50 and 79 years in 2015 and this is expected to increase to 35.6% by 2040. To a great extent, the high

prevalence of T2DM and impaired glucose tolerance are a consequence of the ageing of Europe's population.[22]

In 2017, *the IDF Diabetes Atlas* reported that there were little gender differences in the global number of patients with DM for 2017. There were about 17 million more men than women with diabetes in 2017 (221 million men vs 204 million women).[2] In terms of prevalence, the NCD Risk Factor Collaboration reported global age-standardised sex-specific diabetes prevalence of 9% (7.2–11.1) in men and 7.9% (6.4–9.7) in women in 2014.[33] In terms of incidence, incidence rates have been reported higher for males than for females in most epidemiological studies.[8, 10, 11, 13]

2.1.1.3 Risk factors for the disease

T1DM

The reasons for the increasing number of people who develop T1DM are still unclear and under investigation. Although T1DM mostly occurs in individuals without a family history of the disease, T1DM is highly heritable.[34, 35] The lifetime risk of developing T1DM is 1:20 if a first-degree relative has T1DM compared with 1:300 in the general population.[29] Other risk factors may include the presence of certain genes, and exposure to environmental factors,[36] or changes in environmental risk factors and/or viral infections.[22]

T2DM

The rise in the number of people with T2DM worldwide is associated with ageing populations, economic development, increasing urbanisation, less healthy diets and reduced physical activity.[22] The most important risk factors include overweight or obesity, reduced physical activity/sedentary behaviour, dietary factors, smoking, previously identified (impaired) glucose tolerance (impaired glucose tolerance [IGT] and/or impaired fasting glucose [IFG]), abnormal lipids (elevated triglycerides, low high-density lipoproteins [HDL] cholesterol levels), hypertension, inflammation, intrauterine environment, age, sex, ethnicity, family history of T2DM, history of gestational diabetes and polycystic ovary syndrome.[37] Overweight or obesity are the single most important predictors of T2DM, and the effect of obesity on lifetime risk of T2DM is stronger in younger adults.[37] It has been estimated that the risk of developing T2DM is increased 93-fold in women and 42-fold in men who are severely obese rather than of healthy weight.[38]

2.1.1.4 The main existing treatment options

For people with T1DM, treatment typically includes a carefully calculated diet, planned physical activity, home blood glucose testing several times a day and multiple daily insulin injections. Although diet and exercise are important in the treatment of T1DM, they do not reverse the disease or remove the need for insulin.

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) guidelines for the treatment of hyperglycaemia in T2DM recommend starting with lifestyle

intervention together with metformin as the first pharmacological therapy, if tolerated. Alternatively, other oral agents (e.g., sulfonylurea/glinides, pioglitazone or dipeptidyl peptidase-4 [DPP-4] inhibitors) could be the first anti-diabetic medication. If non-insulin monotherapy at maximal tolerated dosages does not achieve or maintain the HbA_{1c} target, a second oral antidiabetic drug (OAD), glucagon-like peptide-1 (GLP-1) receptor agonist or basal insulin should be added. For further intensification, combination therapy of these and/or intensification of insulin therapy may be considered.[10]

2.1.1.5 Natural history of the indicated condition including mortality and morbidity

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 manifest until the majority of the β-cells are destroyed as there is a gap between the onset of autoimmunity and the onset of diabetes.[39] 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 also destroyed, and the pancreas stops producing sufficient insulin to aid blood glucose 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.[40] T1DM 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.

T2DM

T2DM is a heterogeneous, chronic and 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.[41] The end point 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. DM is a leading cause of end-stage renal disease (ESRD), non-traumatic lower extremity amputations, adult blindness and cardiovascular complications.[41-43]

DM and its complications are also the major causes of early death in most countries. Estimates of the number of deaths caused annually by DM on a global scale are subject to uncertainty, owing in part to the fact that DM is often omitted from death certificates as the cause of death and that

DM-related mortality data are lacking in many countries. The World Health Organization (WHO) has estimated that in 2012 there were 1.5 million deaths worldwide directly caused by DM. It was the eighth leading cause of death among both sexes and the fifth leading cause of death in women in 2012.[44] Rates (per 100,000 by WHO region, age ≥20 years) are the 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.[44] Based on the IDF Atlas, it has been estimated that in 2017, approximately 4.0 million deaths in people in the age group 20–79 years may have been attributable to DM. DM accounted for 10.7% of global all-cause mortality among people in this age group. Close to half (46.1%) of the deaths due to diabetes were in people <60 years.[2]

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 (95% confidence interval [CI], 1.14 to 1.16) and 1.14 (95% CI, 1.13 to 1.15), respectively.[45] Cardiovascular disease is one of the leading causes of death among people with DM and can account for ≥50% of deaths due to DM in some populations.[22] For instance, heart failure survival is worse in the presence of DM.[47] Moreover, the mortality after a first myocardial infarction has remained significantly higher in the diabetic population, in spite of improved survival in both diabetic and non-diabetic patients with incident myocardial infarction (MI) over the past decades.[46-48] Furthermore, higher cancer mortality rates have been observed in patients with diabetes than in non-diabetic patients.[49]

2.1.1.6 Important co-morbidities found in the target population

Patients with DM are at higher risk of developing a number of disabling and life-threatening health problems than people without DM.[22]

An overview of the important co-morbidities found in the target population is shown in Table 2-1.

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

Disorders	Important co-morbidities/complications
Macrovascular disorders	Congestive heart failure, Myocardial infarction, Peripheral arterial disease and Stroke
Microvascular and other disorders	Neuropathy, Nephropathy, Extremity ulcers, Retinopathy, Dyslipidaemia and Hypertension
Neoplasms and cancers	Liver, Pancreas, Colorectal and Breast

2.2 Module SII: Nonclinical safety findings

2.2.1 Important nonclinical safety findings and their relevance to human use

The pharmacology of insulin aspart as fast-acting insulin therapy is well established as the molecule has been administered to subjects with diabetes for more than 15 years.

A summary of important nonclinical findings is given 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
General toxicity studies Hypoglycaemia was observed in all animal species (in severe cases with related death).	Hypoglycaemia is a result of the pharmacodynamic properties of insulin. Hypoglycaemia can be life threatening if severe, and is considered an important identified risk. Severe hypoglycaemia may result in a fatal outcome.
Reproductive toxicity Insulin aspart and human insulin showed similar reproductive effects, which are most likely secondary to maternal hypoglycemia in the non-diabetic animals.	All observed effects are considered secondary to maternal hypoglycemia. Similar effects on reproduction and embryo–foetal development are known to occur in inappropriately treated diabetic women.
Genotoxicity Insulin aspart did not display any mutagenic potential in any of the *in vivo* and *in vitro* mutagenicity studies.	No safety concerns raised
Carcinogenicity studies None of the animal studies indicated an increased carcinogenic potential of insulin aspart compared to human insulin. Insulin aspart and human insulin showed similar effects as in the controls in 52-week studies in rats at doses up to 50 U/kg/day. This dose is approximately 50-fold higher than the expected maximum human dose. At the highest dose levels tested, corresponding to a 100–200-fold higher dose than the expected maximum human dose, both insulin aspart and human insulin were able to induce mammary tumours in female rats.	Carcinogenic potential of insulin aspart is similar to that of human insulin
Injection site tolerability Local tissue reactions in animals were mild and comparable to human insulin preparations.	No safety concerns raised
General safety pharmacology Insulin aspart and human insulin showed similar effects in the wide range of safety pharmacology studies performed.	No safety concerns raised
Mechanisms for drug interactions No classical drug–drug interactions have been reported for human insulin, and it is highly unlikely that co-administration of insulin aspart with other drugs will interact with the principal enzymes of insulin aspart catabolism and thus cause changes in elimination. No *in vitro* studies have been conducted with insulin aspart to assess potential drug–drug interactions. However, a number of products are known to decrease/increase insulin requirements.	No safety concerns raised

Key safety findings (from nonclinical studies)	Relevance to human usage
Other toxicity-related information or data Local toxicity has been evaluated in pigs for biphasic insulin aspart. The extent of local reactions was comparable to human insulin preparations.	No safety concerns raised. Both insulin aspart and biphasic insulin aspart have been widely used clinically and the local tolerability has been evaluated during the clinical development and post-marketing use.

2.2.2 Conclusions on nonclinical data

Based on the toxicological investigations, except for the known risk of hypoglycaemia, all insulin aspart formulations are considered to be safe for chronic human administration.

Table 2-3 Summary of nonclinical 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
Missing information None

Note: The risk of 'hypoglycaemia' has been proposed to be removed from this RMP because this risk is fully characterised and appropriately managed according to the guidance provided in the GVP Module V (Rev 2); see Section 2.7.2.1.

Abbreviations: GVP = Guideline on good pharmacovigilance practices; RMP = risk management plan.

2.3 Module SIII: Clinical trial exposure

Insulin aspart has been on the market since 1999. Although this section is not applicable for insulin aspart (as the primary investigational medicinal product [IMP]) according to the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) based on the well-established medicinal use with over 15 years of post-marketing experience, exposure data from the Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results (LEADER) trial (trial EX2211-3748, with Victoza® [liraglutide] as the primary IMP) has been presented in this section in order to support the proposed indication for NovoMix® 30 (i.e., use of NovoMix® 30 in combination with GLP-1 receptor agonists [Table 1-2]).

LEADER was a long-term, multi-centre, international, randomised double-blind placebo-controlled phase 3b trial for Victoza® to determine the effectiveness and long-term safety of liraglutide on cardiovascular outcomes, in which subjects at high risk of experiencing cardiovascular events were included. The clinical trial report was finalised on 29 Aug 2016, based on which the trial was considered completed.

The main inclusion criteria for the trial included male and female subjects with T2DM, with a glycosylated haemoglobin (HbA_{1c}) of ≥7.0% at screening and who were antidiabetic drug naïve or treated with one or more OADs or treated with human neutral protamine Hagedorn (NPH) insulin or long-acting insulin analogue or premixed insulin, alone or in combination with OADs. This included subjects aged:

- either ≥50 years with at least one of the following criteria: prior myocardial infarction; prior stroke or prior transient ischaemic attack (TIA); prior coronary, carotid or peripheral arterial revascularisation; >50% stenosis on angiography or other imaging of coronary, carotid or lower extremity arteries; history of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging, or unstable angina with electrocardiogram (ECG) changes, asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or dobutamine stress echo; chronic heart failure New York Heart Association (NYHA) class II–III; chronic renal failure, having clinically reached a stage corresponding to a glomerular filtration rate of <60 mL/min/1.73 m^2 per Modification of Diet in Renal Disease (MDRD) or <60 mL/min per Cockroft-Gault formula.
- or ≥60 years with at least one of the following criteria: microalbuminuria or proteinuria; hypertension and left ventricular hypertrophy by ECG or imaging; left ventricular systolic or diastolic dysfunction by imaging; ankle/brachial index <0.9.

Table 2-4 to Table 2-7 show observation time and exposure to liraglutide in subjects with T2DM using NovoMix® at baseline and the following 26 weeks from the LEADER trial.

Table 2-4 Observation time by treatment – subjects using NovoMix® at baseline and the following 26 weeks - full analysis set, LEADER trial

	Lira	Placebo	Total
Number of subjects	219	227	446
Randomised, N (%)			
N	219 (100.0)	227 (100.0)	446 (100.0)
0- 6 Months	0 (0.0)	0 (0.0)	0 (0.0)
6-12 Months	2 (0.9)	4 (1.8)	6 (1.3)
1- 2 Years	6 (2.7)	6 (2.6)	12 (2.7)
2- 3 Years	4 (1.8)	6 (2.6)	10 (2.2)
3- 4 Years	203 (92.7)	209 (92.1)	412 (92.4)
4- 5 Years	4 (1.8)	2 (0.9)	6 (1.3)

Lira: Liraglutide
N: Number of subjects, %: Percentage of subjects
Observation time defined as duration in trial including periods off-treatment with investigational product.

Table 2-5 Proportion of exposure according to dose – subjects using NovoMix® at baseline and the following 26 weeks - full analysis set, LEADER

Dose (mg.)	Lira (%)
0.6	6.8
1.2	10.1
1.8	83.1

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

Table 2-6 Observation time by age group, gender and by treatment – subjects using NovoMix® at baseline and the following 26 weeks - full analysis set, LEADER

T2DM Subjects	Lira N (observation time, PYO)			Placebo N (observation time, PYO)		
Age range	Male	Female	Total	Male	Female	Total
Adults (18-64 years)	70 (253)	32 (115)	102 (368)	74 (261)	48 (169)	122 (431)
Elderly (65-74 years)	60 (211)	26 (95)	86 (305)	50 (183)	29 (106)	79 (289)
Elderly (75-84 years)	15 (51)	13 (47)	28 (98)	13 (43)	11 (37)	24 (81)
Elderly (85+ years)	1 (4)	2 (6)	3 (10)	2 (4)	0	2 (4)
Total	146 (519)	73 (263)	219 (782)	139 (492)	88 (313)	227 (805)

Lira: Liraglutide
N: Number of subjects, T2DM: Type 2 Diabetes Mellitus, PYO: Patient years of observation time.
Observation time defined as duration in trial including periods off-treatment with investigational product.

Table 2-7 Exposure in special populations – subjects using NovoMix® at baseline and the following 26 weeks - full analysis set, LEADER

	Lira N	Placebo N
NYHA Class		
No heart failure		
FAS	**186**	**191**
PYO	**668**	**682**
NYHA class I		
FAS	8	7
PYO	30	25
NYHA class II		
FAS	19	23
PYO	64	82
NYHA class III		
FAS	6	6
PYO	19	16
Renal function (eGFR-MDRD)		
Normal renal function (eGFR-MDRD >=90 ml/min/1.73m^2)		
FAS	63	68
PYO	232	243
Mild renal impairment (eGFR-MDRD >=60 and <90 ml/min/1.73m^2)		
FAS	86	87
PYO	307	313
Moderate renal impairment (eGFR-MDRD >=30 and <60 ml/min/1.73m^2)		
FAS	62	64
PYO	217	219
Severe renal impairment (eGFR-MDRD <30 ml/min/1.73m^2)		
FAS	8	8
PYO	26	30

Lira: Liraglutide
N: Number of subjects, FAS: Full analysis set, NYHA: New York Heart Association, PYO: Patient years of observation
Observation time defined as duration in trial including periods off-treatment with investigational product.
Only (index) events after randomisation are included.
The index event is the event selected among multiple events if these were assessed and confirmed to be one and the same event.
Severe renal impairment: Subjects with eGFR < 30 ml/min/1.73 m^2.
Moderate renal impairment: Subjects with 30 <= eGFR < 60 ml/min/1.73 m^2.
Mild renal impairment: Subjects with 60 <= eGFR < 90 ml/min/1.73 m^2.
Normal renal function: Subjects with eGFR >= 90 ml/min/1.73 m^2.
Events of heart failure and unstable angina pectoris requiring hospitalisation are included in this table.

2.4 Module SIV: Populations not studied in clinical trials

Insulin aspart has been on the market since 1999. This section is, therefore, not applicable according to the GVP Module V – Risk management systems (Rev 2) based on the well-established medicinal use with over 15 years of post-marketing experience.

2.5 Module SV: Post-authorisation experience

2.5.1 Post-authorisation exposure

2.5.1.1 Method used to calculate exposure

Insulin aspart has been on the market since September 1999. The total exposure is expressed as patient-years of exposure (PYE), which is a crude estimate and derived from the total sales volume (in units), including samples of insulin aspart, assuming an average daily consumption of 40 U (defined by the WHO). The figures presented in Table 2-8 are based on a cumulative period starting 01 Jan 2002, because prior to this period, sales figures were registered in a different manner.

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

2.5.1.2 Exposure

NovoRapid® and NovoMix® 30 are older products than NovoMix® 50 and NovoMix® 70 (for the first marketing authorisation status, see Table 2-8). Furthermore, they are launched in around 5 times as many countries, which also helps explain the variation in cumulative exposure between the products seen in Table 2-8.

Table 2-8 Exposure to insulin aspart by product and region

Product	First marketing authorisation in the EU	Cumulative exposure since 2002 (PYE)		
		EU[a]	Non-EU	Total
NovoRapid®	07 Sep 1999	20,472,768	32,464,246	52,937,013
NovoRapid® PumpCart®	19 Dec 2013	75,576	13	75,588
NovoMix® 30	01 Aug 2000	11,563,170	25,134,401	36,697,570
NovoMix® 50	05 Oct 2005	592,863	323,582	916,445
NovoMix® 70	05 Oct 2005	198,286	46,715	245,000
Total		**32,827087**	**57,968,942**	**90,796,029**

Note: The cumulative exposure is based on the data from 01 Jan 2002 onwards; sales figures were not registered in a consistent manner before this date. As the exposure is based on volume distributed to external customers and average daily usage rather than actual patient exposure, the numbers can be over-estimated or under-estimated.

[a]EU 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

As the insulin aspart products are available as prescription only, the potential for off-label use is considered to be low. However, off-label use at the discretion of the prescribing physician cannot be excluded.

Some of the clinical and nonclinical uses of insulin products outside the approved indications are documented in the literature, such as preventing and treating hyperglycaemia in critically ill patients (adults[50-53] and children[54]) in the intensive care unit, treating hyperkalaemia most commonly in combination with glucose (promoting the intracellular uptake of potassium)[55, 56] and enhancing performance of professional athletes and bodybuilders.[57, 58] Additionally, the use of treating overdoses of cardiovascular agents, as high-dose insulin appears to enhance cardiac carbohydrate metabolism and has direct inotropic effects, is supported by various case reports and case series which has arisen due to a lack of authorised alternative treatments.[59, 60] Treatment of specific overdoses (e.g., with calcium channel blockers or beta-blockers)[59, 60] along with other high-dose insulin/euglycaemia (HIE) therapy is included in various toxicology guidelines. However, the precise extent of this use outside the approved indications is unknown.

2.6 Module SVI: Additional EU requirements for the safety specification

2.6.1 Potential for misuse for illegal purposes

As for all insulin products, there is a potential that insulin aspart is misused either by diabetic patients or non-diabetic persons. Examples of misuse are intentional overdoses, suicide attempts and use for anabolic purposes by body builders or endurance athletes.[61-63]

To limit the misuse of insulin aspart within the approved indications/populations, relevant information/risk minimisation measures are included in the Summary of Product Characteristics (SmPC) and package leaflets (PLs) for NovoRapid® and NovoMix®.

2.7 Module SVII: Identified and potential risks

2.7.1 Identification of safety concerns in the initial RMP submission

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

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

No new safety concerns including potential or identified risks for NovoRapid® or NovoMix®, neither in the approved nor in the proposed indications, have been identified. However, safety concerns included in Table 2-9 have been proposed to be reclassified/removed from the list of safety concerns for insulin aspart in this version of the RMP (for details, see Sections 2.7.2.1, 2.7.2.2 and 2.7.2.3).

Table 2-9 Reclassified/removed safety concerns, insulin aspart

Safety concern	Product	Included/classified as (RMP Ed 2, Vs 1)	Reclassified as/removed (RMP version 3.1)
Hypoglycaemia	NovoRapid® and NovoMix® (NovoMix® 30/50/70)	Important identified risk	Proposed to be removed
Systemic allergic reactions	NovoRapid® and NovoMix® (NovoMix® 30/50/70)	Important identified risk	Proposed to be removed
Medication errors	NovoRapid® and NovoMix® (NovoMix® 30/50/70)	Important identified risk	Proposed to be removed
Injection/infusion site reactions in connection with pump use	NovoRapid®	Important potential risk	Removed[a]
Misuse of NovoRapid® PumpCart®	NovoRapid® (NovoRapid® PumpCart® only)	Important potential risk	Removed[a]
Consequences of anti-insulin antibody formation/lack of efficacy	NovoRapid® and NovoMix® (NovoMix® 30/50/70)	Important potential risk	Proposed to be removed
Children <2 years of age/Neonates and infants (<1 year of age)[b]	NovoRapid®	Missing information	Proposed to be removed
Children <10 years of age	NovoMix® 30 only	Missing information	Proposed to be removed
Children and adolescents <18 years of age	NovoMix® 50 and NovoMix® 70	Missing information	Proposed to be removed
Use in pregnant women	NovoMix® (NovoMix® 30/50/70)	Missing information	Proposed to be removed

[a]The EMA PRAC endorsed the MAH's proposal to remove the risks 'Injection/infusion site reactions in connection with pump use' and 'Misuse of NovoRapid® PumpCart®' from the RMP. The risks have therefore been removed based on the assessment report for insulin aspart PSUR covering period 01 Oct 2016–30 Sep 2017 (procedure number: EMEA/H/C/PSUSA/00001749/201709; PRAC recommendation dated 12 Apr 2018).

[b]'Children <2 years of age' was included as missing information for NovoRapid® in the currently approved RMP for insulin aspart (Ed 2, Vs 1, dated 26 Jun 2015). Novo Nordisk obtained approval for use of NovoRapid® in children down to 1 year of age in the EU on 21 Oct 2016.

Abbreviations: EMA = European Medicines Agency; MAH = marketing authorisation holder; PRAC = Pharmacovigilance Risk Assessment Committee; PSUR = periodic safety update report; RMP = risk management plan.

2.7.2.1 NovoRapid® and NovoMix®

Hypoglycaemia

Background

As for other insulin products, hypoglycaemia is the most common undesirable reaction. It may occur if the insulin dose is too high in relation to 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.

Hypoglycaemia is more common in people with T1DM than in people with T2DM, with incidence rates as follows:

- T1DM any/mild/moderate: 15–137 episodes per patient-years[64-71]
- T1DM severe: 0.1–4.9 episodes per patient-years[64-70, 72, 73]
- T2DM any/mild/moderate: 0.2–38.9 episodes per patient-years[68, 69, 74-78]
- T2DM severe: 0–2.5 episodes per patient-years[68, 69, 74-76, 79]

To minimise the probability and severity of the occurrence of hypoglycaemia with insulin aspart, routine risk minimisation measures have been included in the current SmPCs, PLs and instructions for use (IFU); see Table 2-10.

Table 2-10 Summary of risk minimisation measures, Hypoglycaemia

Safety concern ***Product***	**Risk minimisation measures**

Hypoglycaemia
 	
NovoRapid®
	• SmPC Section 4.4 including information on special warnings and precautions for use.
	• SmPC Section 4.5 including information on agents that can potentially mask the symptoms of hypoglycaemia.
	• SmPC Section 4.6 describes that dose adjustment might be needed during pregnancy.
	• SmPC Section 4.7 including information on the ability to drive or operate machinery.
	• SmPC Section 4.8 including information on hypoglycaemia as the most frequently reported ADR and a description of signs and symptoms of hypoglycaemia.
	• SmPC Section 4.9 including information on treatment of hypoglycaemia in case of an insulin overdose.
	• PL Section 2 including information on what can cause hypoglycaemia/low blood sugar, precautions to take and interactions with other medicines and alcohol.
	• PL Section 3 including information on what to do if a patient takes more insulin than required.
	• PL Section 4 describing
	  • low blood sugar (hypoglycaemia) as the most commonly reported ADR
	  • what can cause low blood sugar
	  • signs of low blood sugar
	  • interactions with other agents that can result in too low blood sugar (alcohol)
	  • what to do if low blood sugar is experienced.
	• IFU where the patients are advised:
	  • to read instructions carefully to avoid injecting too little or too much insulin
	  • to check the label to avoid administration of a wrong type of insulin leading to the risk of too low or too high blood sugar
	  • on how to set the dose correctly to avoid high or low blood sugar levels
	  • that a damaged or crushed pen can lead to a too high or low blood sugar.

Safety concern ***Product***	**Risk minimisation measures**

Hypoglycaemia
 	
NovoMix®
	• SmPC Section 4.4 including information on special warnings and precautions for use.
	• SmPC Section 4.5 including information on agents that can potentially mask the symptoms of hypoglycaemia.
	• SmPC Section 4.7 including information on the ability to drive or operate machinery.
	• SmPC Section 4.8 including information on hypoglycaemia as the most frequently reported ADR and a description of signs and symptoms of hypoglycaemia.
	• SmPC Section 4.9 including information on treatment of hypoglycaemia in case of an insulin overdose.
	• PL Section 2 including information on what can cause hypoglycaemia/low blood sugar, precautions to take and interactions with other medicines and alcohol.
	• PL Section 3 including information on what to do if a patient takes more insulin than required.
	• PL Section 4 describing:
	  • low blood sugar (hypoglycaemia) as the most commonly reported ADR
	  • what can cause low blood sugar
	  • signs of low blood sugar
	  • interactions with other agents that can result in too low blood sugar (alcohol)
	  • what to do if low blood sugar is experienced
	• IFU where the patients are advised:
	  • to read instructions carefully to avoid injecting too little or too much insulin
	  • to check the label to avoid administration of a wrong type of insulin leading to the risk of too low or too high blood sugar
	  • on how to set the dose correctly to avoid high or low blood sugar levels
	  • that a damaged or crushed pen can lead to a too high or low blood sugar.

Abbreviations: ADR = adverse drug reaction; IFU = instructions for use; PL = package leaflet; SmPC = Summary of Product Characteristics.

Discussion

An analysis of the data from the vast post-marketing experience of insulin aspart products available in the Novo Nordisk database until the data lock point (DLP) of this RMP was performed (see Table 2-11 and Table 2-12).

A comparison of the cumulative reporting rates (RRs) for hypoglycaemic adverse events (AEs) with NovoRapid® was made for the last three periodic safety update reports/periodic benefit–risk evaluation reports (PSURs/PBRERs; hereafter referred to as PSURs) covering periods 01 Oct 2014–30 Sep 2015, 01 Oct 2015–30 Sep 2016 and 01 Oct 2016–30 Sep 2017 (procedure numbers EMEA/H/C/PSUSA/00001749/201509, EMEA/H/C/PSUSA/00001749/201609 and EMEA/H/C/PSUSA/00001749/201709, respectively). The cumulative RRs have been observed to be increasing over the past 3 years, from 0.16 AEs/1,000 PYE in 2015 to 0.22 AEs/1,000 PYE in 2017. This is similar to the cumulative RR for events reported until the DLP of this RMP (see Table 2-11). As mentioned in the PSURs, the increase in the RR for NovoRapid® is due to a general increase in the number of AEs reported from solicited sources (patient support programmes and market research programmes) and increased reporting from China (where focus from healthcare professionals [HCPs] to report adverse drug reactions (ADRs) has increased and the Chinese Food

and Drug Administration (CFDA) has made bulk releases from its AE database). Overall, no new safety concerns have been identified based on the analysis of these cases.

Table 2-11 Overview of cumulative hypoglycaemic events and reporting rates, by product

Post-marketing events	Number of events			
	NovoRapid®	NovoRapid® PumpCart®	NovoMix® 30	NovoMix® 50 and 70
Total	**11,807**	**195**	**3,718**	**158**
Serious	3,863	77	1,209	85
Non-serious	7,944	118	2,509	73
Exposure in PYE	52,937,013	75,588	36,697,570	1,161,445
Reporting rate of events (events/PYE × 1,000)	**0.22**	**2.58**	**0.10**	**0.14**
Reporting rate of serious events (serious events/PYE × 1,000)	0.07	1.02	0.03	0.07

Note: Narrow scope PTs included in the MedDRA SMQ (Version 20.1) Hypoglycaemia were used to identify relevant events.

Reporting rates (RRs) are given as number of AEs per 1,000 PYE.

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PYE = patient-years of exposure; RR = reporting rate; SMQ = standardised MedDRA query.

The RR of hypoglycaemic AEs with NovoRapid® PumpCart® is, apparently, higher than that with the other insulin aspart products. As the insulin used in NovoRapid® PumpCart® is the same as that used in other NovoRapid® presentations, it is unlikely that the higher RR is due to the insulin. Based on the reported medications errors (see sub-heading 'Medication errors' under this section), which primarily concern faulty mounting of the PumpCart® cartridge in the insulin pump (which can lead to hyperglycaemia [but not hypoglycaemia]), it is unlikely that the higher RR is due to medication errors. It is, therefore, evaluated that the higher RR is most likely due to patients and relatives being more alert and prone to reporting AEs when initiating a new type of treatment. NovoRapid® PumpCart®, being a relatively newer product as compared to the other insulin aspart products, is most likely to have more new patients.

For all NovoMix® products, the RRs of hypoglycaemic AEs have not changed significantly since 01 Oct 2014–31 Jan 2018 (i.e., over periods covered by the last 3 PSURs until the DLP of this RMP).

The majority of hypoglycaemic AEs (67%) are non-serious for all insulin aspart products. An informative analysis based on the severity of post-marketing hypoglycaemic AEs has been precluded as 83% of the AEs do not have severity reported.

The majority of hypoglycaemic AEs were reported with the outcome 'recovered' or 'recovering' for NovoRapid® (61%), NovoMix® 30 (58%) and NovoMix® 50/70 (68%). For NovoRapid® PumpCart®, approximately half of the hypoglycaemic AEs were reported with the outcome 'recovered' or 'recovering'. The remaining half had outcome 'unknown'; only few events were reported with other outcomes. The fraction of hypoglycaemic AEs with outcomes 'fatal' and 'recovered with sequelae' was low (Table 2-12).

Table 2-12 Overview of hypoglycaemic events with severe event outcomes, by product

Product	Event outcome	
	Fatal N (%)	Recovered with sequelae N (%)
NovoRapid®	39 (0.33%)	40 (0.34%)
NovoRapid® PumpCart®	1 (0.51%)	1 (0.51%)
NovoMix® 30	12 (0.32%)	19 (0.51%)
NovoMix® 50/70	1 (0.63%)	1 (0.63%)

Abbreviations: N = number of events; % = percentage of events.

As mentioned in the last PSUR (covering period 01 Oct 2016–30 Sep 2017), the frequency and distribution of hypoglycaemic AEs (both serious and non-serious) were comparable to the incidence rates based on the epidemiological data and literature. Based on an evaluation of cumulative cases concerning hypoglycaemic events, no new safety concerns have been identified for insulin aspart. Furthermore, Novo Nordisk assesses that the risk of hypoglycaemia for insulin aspart is fully characterised and appropriately managed. Although hypoglycaemia remains the most common adverse effect for all insulins, the risk minimisation messages included in the product information are considered adequate to inform prescribers on safe and appropriate use of the products.

Conclusion

Novo Nordisk proposes to remove the risk of hypoglycaemia from the RMP for insulin aspart because this risk is fully characterised and appropriately managed according to the guidance provided in the GVP Module V (Rev 2). 'Hypoglycaemia' is still considered an important risk relevant for the benefit–risk profile of insulin aspart and will be monitored through routine pharmacovigilance activities, including single case reporting, PSURs and signal detection. Any new relevant information will be presented in the PSURs.

Systemic allergic reactions

Background

Allergic reactions, ranging in severity from mild to severe, can occur after contact with an allergen. Repeated exposure to an allergen may lead to generalised hypersensitivity and more serious reactions with the most severe being anaphylaxis. Common symptoms of a mild allergic reaction can include skin manifestations such as rashes and itching. Symptoms of a moderate to severe

reaction can include a generalised skin rash (urticaria), itching, fever, sweating, nausea/vomiting, angioedema, difficulties in breathing, palpitations and a drop in blood pressure. Generalised hypersensitivity reactions with severe, anaphylactic symptoms are potentially life threatening.

The prevalence of insulin allergy has decreased with the use of recombinant insulin. However, local reactions to the most recent formulations of insulin continue to be observed, but are infrequent, and systemic reactions are rare.[80, 81]

The overall prevalence of allergic reactions to insulin products was observed to have decreased from as many as 50–60%[82] to less than 0.1–3%,[82, 83] and less than one-third of these events have been considered related to insulin itself.[81, 84] Other reactions occur due to preservatives added to insulin.[81, 82]Many case reports have been reported in the literature,[85, 86] but the frequency of specific insulin allergic reactions is largely unknown.[81, 82] 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.[87] Interestingly, continuous subcutaneous insulin infusion (CSII) in combination with short-acting analogues seems to reduce insulin allergy and has been used successfully as the method of desensitisation in the treatment of localised and generalised hypersensitivity reactions in diabetic patients with insulin allergy.[82]

To minimise the probability and severity of the occurrence of systemic allergic reactions with insulin aspart, routine risk minimisation measures have been included in the current SmPCs, PLs and IFU; see Table 2-13.

Table 2-13 Summary of risk minimisation measures, Systemic allergic reactions

Safety concern ***Product***	**Risk minimisation measures**
Systemic allergic reactions *NovoRapid®*	• SmPC Section 4.3 including information on contraindications in case of hypersensitivity to the active substance or any of the excipients. • SmPC Section 4.8 including information on anaphylactic reactions as potentially life-threatening side effect, and their signs and symptoms. • PL Section 2 including information on when not to use the insulin (e.g., if the patient is allergic to insulin aspart or other ingredients [listed in Section 6 of PL]). • PL Section 4 including information on serious allergic reactions as potentially life–threatening side effect, and the signs and symptoms.
Systemic allergic reactions *NovoMix®*	• SmPC Section 4.3 including information on contraindications in case of hypersensitivity to the active substance or any of the excipients. • SmPC Section 4.8 including information on anaphylactic reactions as potentially life-threatening side effect, and their signs and symptoms. • PL Section 2 including information on when not to use the insulin (e.g., if the patient is allergic to insulin aspart or other ingredients [listed in Section 6 of PL]). • PL Section 4 including information on serious allergic reactions as potentially life-threatening side effect, and the signs and symptoms.

Abbreviations: IFU = instructions for use; PL = package leaflet; SmPC = Summary of Product Characteristics.

Discussion

An analysis of the data from the vast post-marketing experience of insulin aspart products available in the Novo Nordisk database until the DLP of this RMP was performed (see Table 2-14 and Table 2-15).

Table 2-14 Overview of cumulative events and reporting rates concerning systemic allergic reactions, by product

Post-marketing events	Number of events			
	NovoRapid®	NovoRapid® PumpCart®	NovoMix® 30	NovoMix® 50 and 70
Total	**3,113**	**14**	**2,060**	**50**
Serious	505	3	384	7
Non-serious	2,608	11	1,676	43
Exposure in PYE	52,937,013	75,588	36,697,570	1,161,445
Reporting rate of events (events/PYE × 1,000)	**0.06**	**0.19**	**0.06**	**0.04**
Reporting rate of serious events (serious events/PYE × 1,000)	0.010	0.040	0.010	0.006

Note: Narrow scope PTs included in the MedDRA SMQs (Version 20.1) Anaphylactic reaction, Angioedema, Anaphylactic/Anaphylactoid shock conditions, Hypersensitivity and Severe cutaneous adverse reactions were used to identify relevant events.

Reporting rates (RRs) are given as number of AEs per 1,000 PYE.

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PYE = patient-years of exposure; RR = reporting rate; SMQ = standardised MedDRA query.

A comparison of the cumulative RRs for AEs concerning systemic allergic reactions with insulin aspart was made for the last three PSURs covering periods 01 Oct 2014–30 Sep 2015, 01 Oct 2015–30 Sep 2016 and 01 Oct 2016–30 Sep 2017 (procedure numbers EMEA/H/C/PSUSA/00001749/201509, EMEA/H/C/PSUSA/00001749/201609 and EMEA/H/C/PSUSA/00001749/201709, respectively). For all insulin aspart products, the cumulative RRs for events potentially associated with systemic allergic reactions were observed to be similar in the last 3 PSUR periods. This is also observed to be similar to the cumulative RR for events reported until the DLP of this RMP (Table 2-14).

The higher RR observed with NovoRapid® PumpCart® is unlikely related to the insulin, which is the same as used in the other NovoRapid® presentations. The total number of events reported with NovoRapid® PumpCart® was low (Table 2-14), and no safety concerns were identified based on review of these cases.

The fraction of AEs concerning potential systemic allergic reactions with outcomes 'fatal' and 'recovered with sequelae' was low (see Table 2-15).

Table 2-15 Overview of severe event outcomes concerning systemic allergic reactions, by product

Product	Event outcome	
	Fatal N (%)	Recovered with sequelae N (%)
NovoRapid®	6 (0.19%)	7 (0.22%)
NovoRapid® PumpCart®	0 (0.00%)	0 (0.00%)
NovoMix® 30	3 (0.15%)	12 (0.58%)
NovoMix® 50/70	0 (0.00%)	0 (0.00%)

Abbreviations: N = number of events; % = percentage of events.

Novo Nordisk assesses that the risk of systemic allergic reactions for insulin aspart is fully characterised and appropriately managed. Although systemic allergic reactions remain a potentially fatal adverse effect for all insulins, insulin aspart has a well-established safety profile with over 15 years of post-marketing experience. The risk of systemic allergic reactions is being monitored by routine pharmacovigilance activities, including single case reporting, PSURs and signal detection. The routine risk mitigation measures concerning allergic reactions are considered sufficient (see Table 2-13). Based on the analysis of the safety data (including serious cases) reported in patients using insulin aspart (wherein no unexpected clusters of AEs concerning the risks were identified), no new safety concerns for insulin aspart have been identified. Specific clinical measures to address this risk are fully integrated into standard clinical practice and are known to both the patients and the HCPs. Therefore, it is assessed that the risk of systemic allergic reactions does not need additional risk minimisation activities beyond the planned routine pharmacovigilance activities.

Conclusion

Novo Nordisk proposes to remove the risk of systemic allergic reactions from the RMP for insulin aspart because this risk is fully characterised and appropriately managed according to the guidance provided in the GVP Module V (Rev 2). 'Systemic allergic reactions' is still considered an important risk relevant for the benefit–risk profile of insulin aspart, and will be monitored through routine pharmacovigilance activities, including single case reporting, PSURs and signal detection. Any new relevant information will be presented in the PSURs.

Medication errors

Background

Medication errors are a known risk for many insulins. The administration of a wrong dose or the administration of a wrong type of insulin can occur due to a mix-up by the patient, a mix-up by a healthcare professional in a clinical setting, a prescription error or a dispensing error at the pharmacy. Storing the product with an attached needle can lead to leakage of insulin and the appearance of an air gap between the piston rod and the cartridge. If the device is not primed as described in the user information, this may lead to underdosing of insulin and consequently poor

glycaemic control. In addition, re-use of the needles may lead to painful injections due to blunt/blocked needles.

Medication errors with insulin could lead to serious consequences and could potentially be fatal, for instance, in case of administering the wrong type of insulin. Events of medication errors leading to serious reactions which require hospitalisation impose demands on healthcare resources. For example, a mix-up between insulin products could potentially cause the patient to develop severe dysglycaemia.

To minimise the probability and severity of the occurrence of hypoglycaemia with insulin aspart, routine risk minimisation measures have been included in the current SmPCs, PLs and instructions for use (IFU); see Table 2-16.

Table 2-16 Summary of risk minimisation measures, Medication errors

Safety concern ***Product***	**Risk minimisation measures**
Medication errors *NovoRapid®*	• SmPC Section 4.2 where information is given on posology and method of administration. • SmPC Section 4.2 where passive discouragement for withdrawing insulin with a syringe from cartridges and prefilled pens is included. It is specified that NovoRapid® vial can be used if intravenous administration is applicable. It also clarifies that NovoRapid® vial and NovoRapid® PumpCart® can be used for CSII. • SmPC Section 4.4 where information is given on the avoidance of medication errors. • SmPC Section 6.4 where special precautions for storage are given. • SmPC Section 6.6 where special precautions are given for disposal and other handling. Text/wording allowing the possibility to withdraw insulin from cartridges and prefilled pens with a syringe in case of emergency has been deleted from this section. • PL Section 2 with information on when the medicine should not be used, and also to check the label before use to ensure the right type of medicine is used. • PL Section 3 with information on how to use the product and to carry a spare cartridge (Penfill® and PumpCart®). • PL Sections 2 and 3 where passive discouragement for withdrawing insulin with a syringe from cartridges and prefilled pens is included. • PL Section 5 with information on how to store the product and warning for unintended use by children. • IFU where information is given on how to handle the product including instruction to check the label to ensure the right type of insulin is used and instruction on how to avoid injection of air to ensure proper dosing and to carry a spare prefilled pen in case it is lost or damaged. • Product differentiation strategy includes trade names, label text, colour branding of the carton and container label.

Safety concern *Product*	Risk minimisation measures
Medication errors *NovoMix®*	• SmPC Section 4.2 where information is given on posology and method of administration. • SmPC Section 4.2 where passive discouragement for withdrawing insulin with a syringe from cartridges and prefilled pens is included. • SmPC Section 4.4 where information is given on the avoidance of medication errors. • SmPC Section 6.4 where special precautions for storage are given. • SmPC Section 6.6 where special precautions are given for disposal and other handling. • PL Section 2 with information on when the medicine should not be used, and also to check the label before use to ensure the right type of medicine is used. • PL Section 3 with information on how to use the product and to carry a spare cartridge (Penfill®). • PL Sections 2 and 3 where passive discouragement for withdrawing insulin with a syringe from cartridges and prefilled pens is included. • PL Section 5 with information on how to store the product and warning for unintended use by children. • IFU where information is given on how to handle the product including instruction to check the label to ensure the right type of insulin is used and instruction on how to avoid injection of air to ensure proper dosing and to carry a spare prefilled pen in case it is lost or damaged. • Product differentiation strategy includes trade names, label text, colour branding of the carton and container label. • The PL also contains information on resuspending the insulin every time a new NovoMix® Penfill® is used. It is recommended to always check if there is enough insulin left (at least 12 units) in the cartridge to allow even resuspension, and to use a new one if there is not enough insulin left.

Abbreviations: IFU = instructions for use; PL = package leaflet; SmPC = Summary of Product Characteristics.

Discussion

An analysis of the data from the vast post-marketing experience of insulin aspart products available in the Novo Nordisk database until the DLP of this RMP was performed (see Table 2-17 to Table 2-21).

Table 2-17 Overall medication errors: Overview of cumulative events from post-marketing experience, by seriousness

Post-marketing events	Number of events			
	NovoRapid®	NovoRapid® PumpCart®	NovoMix® 30	NovoMix® 50 and 70
Total	**7,118**	**116**	**2,315**	**32**
Serious	618	15	159	4
Non-serious	6,500	101	2,156	28
Exposure in PYE	52,937,013	75,588	36,697,570	1,161,445
Reporting rate of events (events/PYE × 1,000)	**0.13**	**1.53**	**0.06**	**0.03**

Note: Narrow scope PTs included in the MedDRA SMQ (Version 20.1) Medication error were used to identify relevant events. Reporting rates (RRs) are given as number of AEs per 1,000 PYE.

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PYE = patient-years of exposure; RR = reporting rate; SMQ = standardised MedDRA query.

Table 2-18 Overall medication errors: Overview of cumulative events from post-marketing experience, by severe case outcome

Product	Case outcome	
	Fatal N (%)	Recovered with sequelae N (%)
NovoRapid®	17 (0.24%)	12 (0.17%)
NovoRapid® PumpCart®	1 (0.86%)	1 (0.86%)
NovoMix® 30	8 (0.35%)	1 (0.04%)
NovoMix® 50 and 70	0 (0.00%)	0 (0.00%)

Abbreviations: N = number of events; % = percentage of events.

The fraction of medication error cases with outcomes 'fatal' and 'recovered with sequelae' was low (see Table 2-18 and Table 2-20).

Table 2-19 Identified mix-ups: Overview of cumulative cases and events

Product	Number of cases	Number of events	Reporting rate of events (events/PYE × 1,000)
NovoRapid®	1,161	1,179	0.022
NovoRapid® PumpCart®	1	1	0.013
NovoMix® 30	329	329	0.009
NovoMix® 50 and 70	6	6	0.005

Note: Patient mix-up cases were identified with the PT Wrong drug administered.

Abbreviations: PT = preferred term; PYE = patient-years of exposure.

Table 2-20 Identified mix-ups: Overview of cumulative events from post-marketing experience, by severe case outcome

Product	Case outcome	
	Fatal N (%)	Recovered with sequelae N (%)
NovoRapid®	5 (0.43%)	1 (0.09%)
NovoRapid® PumpCart®	0 (0.00%)	0 (0.00%)
NovoMix® 30	0 (0.00%)	0 (0.00%)
NovoMix® 50 and 70	0 (0.00%)	0 (0.00%)

Note: Percentages are calculated in relation to all cases related to patient mix-ups.

Abbreviations: N = number of events.

Table 2-21 Identified mix-ups: Overview of cases and events co-reported with medical consequences

Product	Number of mix-up cases co-reported with events concerning medical consequence of identified mix-ups	Number of co-reported events concerning medical consequence of identified mix-ups
NovoRapid®	3,949	4,820
NovoRapid® PumpCart®	106	133
NovoMix® 30	1,049	1,230
NovoMix® 50 and 70	18	26

Note: Events concerning medical consequence of identified mix-ups include hypoglycaemia, hyperglycaemia and lack of efficacy events.

The vast majority of events captured by the SMQ Medication errors were non-serious:

- NovoRapid®: 93% non-serious in the reporting period vs. 91% non-serious cumulatively
- NovoMix® 30: 95% non-serious in the reporting period vs. 94% non-serious cumulatively
- NovoMix® 50 and 70: 100% non-serious in the reporting period vs. 88% cumulatively.

Based on an evaluation of cumulative cases concerning medication errors, no new safety concerns have been identified for insulin aspart. Furthermore, Novo Nordisk assesses that the risk of medication errors for insulin aspart is fully characterised and appropriately managed by routine activities and risk minimisation measures already in place. Further evaluations as part of the pharmacovigilance plan through additional pharmacovigilance activities or risk minimisation through additional measures are not considered necessary.

Conclusion

Based on the safety data available for insulin aspart in the Novo Nordisk safety database and considerations that the risk of 'Medication errors' is fully characterised and appropriately managed, it is evaluated that removal of this risk from the RMP (according to the guidance provided in the GVP Module V [Rev 2]) is warranted. Medication errors will be monitored through routine pharmacovigilance activities, including single case reporting, PSURs and signal detection. Any new relevant information will be presented in the PSURs.

Consequences of anti-insulin antibody formation/lack of efficacy

Background

IAsp may, like any other protein or polypeptide, have the potential to be immunogenic in humans, and anti-IAsp antibody formation is a potential reaction with this protein-based drug.

In rare cases, anti-insulin antibodies that target the receptor-binding moiety of the insulin molecule may be produced, potentially resulting in the neutralisation of the effects of insulin. The main clinical observation of this would be lack of efficacy, leading to hyperglycaemia or an unexpected

need to increase the insulin dose. Although spontaneous development of insulin antibodies can occur and may occasionally disturb the glycaemic control in diabetic patients, the evidence is inconclusive.[80] If hyperglycaemia persists and is severe, it can develop into diabetic ketoacidosis; however, the incidence is low at the recommended doses.

To minimise the probability and severity of the occurrence of hypoglycaemia with insulin aspart, routine risk minimisation measures have been included in the current SmPCs, PLs and IFU; see Table 2-22.

Table 2-22 Summary of risk minimisation measures, Consequences of anti-insulin antibody formation/lack of efficacy

Safety concern ***Product***	**Risk minimisation measures**
Consequences of anti-insulin antibody formation/lack of efficacy *NovoRapid®*	• Section 4.4 of the SmPC wherein information on the potential risk of developing antibodies is included
Consequences of anti-insulin antibody formation/lack of efficacy *NovoMix®*	• Section 4.4 of the SmPC wherein information on the potential risk of developing antibodies is included.

Abbreviations: SmPC = Summary of Product Characteristics.

Discussion

An analysis of the post-marketing data for insulin aspart available in the Novo Nordisk database until the DLP of this RMP was performed (see Table 2-23 and Table 2-24).

Table 2-23 Overview of cumulative events from post-marketing experience until the DLP, by seriousness

Post-marketing events	Number of events			
	NovoRapid®	NovoRapid® PumpCart®	NovoMix® 30	NovoMix® 50 and 70
Total	**367**	**0**	**274**	**17**
Serious	208	0	136	7
Non-serious	159	0	138	10
Exposure in PYE	52,937,013	75,588	36,697,570	1,161,445
Reporting rate of events (events/PYE × 1,000)	**0.01**	**0.00**	**0.01**	**0.01**

Note: Relevant cases with antibodies were identified by using the search criteria, including MedDRA PTs (Version 20.1) Anti-insulin antibody, Anti-insulin antibody increased, Anti-insulin antibody positive, Antibody test, Antibody test abnormal, Antibody test positive, Autoantibody positive, Autoantibody test, Drug specific antibody present, Inhibiting antibodies, Neutralising antibodies, Neutralising antibodies positive and Non-neutralising antibodies positive.

Among the cases identified by the above-mentioned search criteria, cases containing co-reported events potentially associated with lack of efficacy were also identified. The search criteria used for identifying antibody cases with co-reported events concerning potential consequences of antibody formation/related to lack of efficacy included the SMQs Hypoglycaemia (narrow terms), Hyperglycaemia/new onset diabetes mellitus (narrow terms) and Lack of efficacy/effect (narrow terms).

Reporting rates are given as the number of AEs per 1,000 PYE.

Abbreviations: AE = adverse event; DLP = data lock point; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PYE = patient-years of exposure; RR = reporting rate; SMQ = standardised MedDRA query.

Limited information is available on the severity of the events reported from post-marketing sources; hence, an informative analysis has been precluded.

The frequency of AEs potentially related to antibody formation was low for all insulin aspart products. The most commonly reported case outcomes were 'recovered' and 'recovering/resolving'. The fraction of cases with outcome 'recovered with sequelae' was low; no cases with outcome 'fatal' were reported.

Table 2-24 Overview of cumulative cases from post-marketing experience until the DLP, by severe case outcome

Product	Case outcome	
	Fatal N (%)	Recovered with sequelae N (%)
NovoRapid®	0 (0%)	2 (0.97%)
NovoRapid® PumpCart®	0 (0%)	0 (0%)
NovoMix® 30	0 (0%)	1 (0.62%)
NovoMix® 50 and 70	0 (0%)	0 (0%)

Note: Percentages are calculated in relation to all cases reporting antibody formation potentially associated with lack of efficacy.

Abbreviations: % = percentage of events; DLP = data lock point; N = number of events.

Based on an evaluation of cumulative cases concerning anti-insulin antibody formation/lack of efficacy, no new safety concerns have been identified for insulin aspart. Furthermore, Novo Nordisk assesses that the risk 'Consequences of anti-insulin antibody formation/lack of efficacy' for insulin aspart is fully characterised and appropriately managed by routine pharmacovigilance activities and risk minimisation measures already in place. Further evaluations as part of the pharmacovigilance plan through additional pharmacovigilance activities or risk minimisation through additional measures are not considered necessary.

Conclusion

Based on the safety data available for insulin aspart in the Novo Nordisk safety database and considerations that the risk of 'Consequences of anti-insulin antibody formation/lack of efficacy' is fully characterised and appropriately managed, it is evaluated that removal of this risk from the RMP (according to the guidance provided in the GVP Module V [Rev 2]) is warranted. The risk will be monitored through routine pharmacovigilance activities, including single case reporting, PSURs and signal detection. Any new relevant information will be presented in the PSURs.

2.7.2.2 NovoRapid®

Injection/infusion site reactions in connection with pump use

Background

NovoRapid® given alone can be used for CSII in pump systems. In this case, NovoRapid® will cover both the bolus insulin requirement (50–70%) and basal insulin rate (30–50%).

NovoRapid® PumpCart® is only for use in an insulin infusion pump system which is designed to be used with this cartridge, such as Accu-Chek® Insight and YpsoPump® Insulin Pump. Injection/infusion site reactions may occur with the use of the pump system. Symptoms may include pain, redness, hives, inflammation, swelling and itching. The exact type of local reaction is difficult to identify, and most reactions are mild and self-limited.[80] Continuous rotation of the

injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection/infusion site reactions may require discontinuation of insulin aspart.

Injection/infusion site reactions may also occur with other insulin aspart presentations, used outside of the context of a pump. However, these are not considered important risks. Injection/infusion site reactions in connection with all insulin aspart products are monitored through routine pharmacovigilance activities.

Epidemiological data for injection/infusion site reactions in CSII patients is limited. A study in T1DM children and adolescent patients with insulin pumps reported a prevalence of cutaneous AE of 4%.[88] Studies on T1DM patients being treated by modern insulin pump therapy (CSII) reported the prevalence of lipohypertrophy to be between 20% and 26%.[89, 90]

Discussion

Injection/infusion site reactions may occur not only with the use of the pump system but also with insulins used outside of a pump. These reactions could be caused by failure to rotate the infusion site within a given area, especially in patients with known allergy to insulin products or other allergies. The public health impact is considered to be minimal as most of the reported events were non-serious.

Due to the relatively small number of injection/infusion site reactions reported in connection to pump use both for NovoRapid® and NovoRapid® PumpCart® from the post-marketing setting compared to the total exposure, combined with the low impact these events would have on the individual patient and the public health, Novo Nordisk proposed to re-classify the risk of injection/infusion site reactions in connection with pump use from an important potential risk to a potential risk for NovoRapid® in the PSUR (covering period 01 Oct 2016–30 Sep 2017; procedure number EMEA/H/C/PSUSA/00001749/201709) submitted to the European Medicines Agency (EMA) in December 2017. No update to current product label and patient information leaflet (PIL) was considered warranted as the current information is considered adequate and sufficient for both HCPs and patients.

Based on the data presented in the PSUR covering the period 01 Oct 2016–30 Sep 2017 and the subsequent response to the request for supplementary information (received with the Pharmacovigilance Risk Assessment Committee [PRAC] Rapporteur's preliminary assessment report on 13 Feb 2018) submitted to the EMA on 14 Mar 2018, the EMA PRAC endorsed the proposal to remove the important potential risk 'Injection/infusion site reactions in connection with pump use' from the RMP (procedure number: EMEA/H/C/PSUSA/00001749/201709; PRAC recommendation dated 12 Apr 2018).

Conclusion

The important potential risk 'Injection/infusion site reactions in connection with pump use' has been removed from the RMP, based on the PRAC recommendation dated 12 Apr 2018 (procedure number: EMEA/H/C/PSUSA/00001749/201709).

Misuse of NovoRapid® PumpCart®

Background

The risk 'Misuse of NovoRapid® PumpCart®' is applicable for NovoRapid® PumpCart® only.

It is possible to fit the 1.6 mL NovoRapid® PumpCart® cartridge into non-Novo Nordisk durable pens and into the D-Tron insulin pump (manufactured by Roche Diagnostics and currently on the market in very low volumes). The NovoRapid® PumpCart® is clearly shorter than other insulin cartridges and this difference could be noted by the end user. However, using a dosing system designed for a 3 mL standard cartridge can result in a 10% underdose. This misuse of NovoRapid® PumpCart® is described in the product labelling.

The following barriers have been implemented to minimise the risk of misuse of NovoRapid® PumpCart® in pen injection systems/pumps not intended for use with NovoRapid® PumpCart®:

- NovoRapid® PumpCart® is significantly shorter than the pen cartridges and an extra effort is required to insert the cartridge in a pen injection device designed for a 3 mL cartridge.
- NovoRapid® PumpCart® has a smaller diameter which will hinder mounting in a pen injection device.
- NovoRapid® PumpCart® appears on the carton as a suffix to the NovoRapid® name to distinguish it from other presentations of NovoRapid®.
- NovoRapid® PumpCart® is significantly shorter than the 3 mL cartridge and an extra effort is required to insert the cartridge in a D-Tron pump designed for a 3 mL Eli Lilly cartridge.
- NovoRapid® PumpCart® has a smaller diameter than the 3 mL Eli Lilly cartridge which will complicate the insertion into the D-Tron insulin pump.

Discussion

The use of NovoRapid® PumpCart® into non-Novo Nordisk durable pens and into the unintended insulin pumps may result in underdosing. The impact on the individual patient may range from no impact to complete lack of efficacy (thereby leading to uncontrolled diabetes).

No case reports concerning use of NovoRapid® PumpCart® into non-Novo Nordisk durable pens and unintended insulin pumps have been received from post-marketing sources since the launch of NovoRapid® PumpCart® in 2014 until the DLP of the this RMP. The risk is being monitored by routine pharmacovigilance activities, including single case reporting, PSURs and signal detection. The product labelling (SmPC/PL) specifically includes instructions on the appropriate and correct use of NovoRapid® PumpCart®; the current risk minimisation measures concerning misuse of

NovoRapid® PumpCart® are considered sufficient. Novo Nordisk proposed to remove the important potential risk of 'Misuse of NovoRapid® PumpCart®' for insulin aspart in the PSUR covering the period 01 Oct 2016–30 Sep 2017, while no updates to the product information were considered warranted.

Based on the data presented in the PSUR covering the period 01 Oct 2016–30 Sep 2017, the PRAC endorsed the proposal to remove the important potential risk 'Misuse of NovoRapid® PumpCart®' from the RMP (procedure number: EMEA/H/C/PSUSA/00001749/201709; PRAC recommendation dated 12 Apr 2018).

Conclusion

The important potential risk 'Misuse of NovoRapid® PumpCart®' has been removed from the RMP, based on the PRAC recommendation dated 12 Apr 2018 (procedure number: EMEA/H/C/PSUSA/00001749/201709).

Children <2 years of age/Neonates and infants (<1 year of age)

Background

'Children <2 years of age' is included as missing information for NovoRapid® in the currently approved RMP for insulin aspart (Edition 2, Version 1, dated 26 Jun 2015). Novo Nordisk obtained approval for use of NovoRapid® in children down to 1 year of age in the EU on 21 Oct 2016, based on which use of NovoRapid® in children between 1 and 2 years is no longer considered to be missing information. Accordingly, missing information concerning 'Children <2 years of age' for NovoRapid® was modified to 'Neonates and infants (<1 year of age)'.

Discussion

Children <1 year of age, including neonates and infants, were excluded from the clinical development programme for insulin aspart.

According to the requirements in GVP Module V – Risk management systems (Rev.2), *missing information for the purpose of the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation or for use in particular patient populations* ***within the approved indication****, for which there is insufficient medicinal product exposure to determine whether the safety profile differs from that characterised so far (see GVP Module V section V.A.1). For example: Use in subpopulations not studied (e.g. exclusion of a subpopulation from clinical studies) but* ***within the approved indication****: the absence of data itself does not automatically constitute a safety concern.*

Conclusion

According to the requirements in GVP Module V – Risk management systems (Rev.2), population excluded from clinical trials should be included as missing information only when they are relevant

for the approved and proposed indications (i.e., *on label*). Therefore, Novo Nordisk proposes to remove the missing information concerning 'Neonates and infants (<1 year of age)' from the RMP for insulin aspart.

2.7.2.3 NovoMix®

Children <10 years of age

Background

'Children <10 years of age' is included as missing information for NovoMix® 30 in the currently approved RMP for insulin aspart (Edition 2, Version 1, dated 26 Jun 2015).

Discussion

Children <10 years of age were excluded from the clinical development program for NovoMix® 30.

According to the requirements in GVP Module V – Risk management systems (Rev.2), *missing information for the purpose of the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation or for use in particular patient populations* ***within the approved indication****, for which there is insufficient medicinal product exposure to determine whether the safety profile differs from that characterised so far (see GVP Module V section V.A.1). For example: Use in subpopulations not studied (e.g. exclusion of a subpopulation from clinical studies) but* ***within the approved indication****: the absence of data itself does not automatically constitute a safety concern.*

Conclusion

According to the requirements in GVP Module V – Risk management systems (Rev.2), population excluded from clinical trials should be included as missing information only when they are relevant for the approved and proposed indications (i.e., *on label*). Therefore, Novo Nordisk proposes to remove the missing information concerning 'Children <10 years of age' from the RMP for insulin aspart.

Children and adolescents <18 years of age

Background

'Children and adolescents <18 years of age' is included as missing information for NovoMix® 50 and NovoMix® 70 in the currently approved RMP for insulin aspart (Edition 2, Version 1, dated 26 Jun 2015).

Discussion

Children and adolescents <18 years of age were excluded from the clinical development program for NovoMix® 50 and NovoMix® 70.

According to the requirements in GVP Module V – Risk management systems (Rev.2), *missing information for the purpose of the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation or for use in particular patient populations* ***within the approved indication****, for which there is insufficient medicinal product exposure to determine whether the safety profile differs from that characterised so far (see GVP Module V section V.A.1). For example: Use in subpopulations not studied (e.g. exclusion of a subpopulation from clinical studies) but* ***within the approved indication****: the absence of data itself does not automatically constitute a safety concern.*

Conclusion

According to the requirements in GVP Module V – Risk management systems (Rev.2), population excluded from clinical trials should be included as missing information only when they are relevant for the approved and proposed indications (i.e., *on label*). Therefore, Novo Nordisk proposes to remove the missing information concerning 'Children and adolescents <18 years of age' from the RMP for insulin aspart.

Use in pregnant women

Background

'Use in pregnancy' is included as missing information for NovoMix® 30, NovoMix® 50 and NovoMix® 70 in the currently approved RMP for insulin aspart (Edition 2, Version 1, dated 26 Jun 2015).

Discussion

Pregnant women were excluded from the clinical development program for NovoMix®.

According to the requirements in GVP Module V – Risk management systems (Rev.2), *missing information for the purpose of the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation or for use in particular patient populations* ***within the approved indication****, for which there is insufficient medicinal product exposure to determine whether the safety profile differs from that characterised so far (see GVP Module V section V.A.1). For example: Use in subpopulations not studied (e.g. exclusion of a subpopulation from clinical studies) but* ***within the approved indication****: the absence of data itself does not automatically constitute a safety concern.*

Conclusion

According to the requirements in GVP Module V – Risk management systems (Rev.2), population excluded from clinical trials should be included as missing information only when they are relevant for the approved and proposed indications (i.e., *on label*). Therefore, Novo Nordisk proposes to remove the missing information concerning 'Use in pregnant women' from the RMP for insulin aspart.

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

2.7.3.1 Important identified and potential risks

There are no risks/missing information included in the safety specification as all the important risks are well described in the proposed product information and appropriately managed by routine pharmacovigilance activities and risk minimisation measures. Therefore, this section is not applicable.

2.7.3.2 Missing information

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

2.8 Module SVIII: Summary of safety concerns

An overview of the safety concerns at the DLP of this RMP is provided in Table 2-25.

Table 2-25 Summary of safety concerns, insulin aspart

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

3 Pharmacovigilance plan

The safety profile of insulin aspart is well defined. Based on the clinical experience and the analysis of all safety data available at the present stage for insulin aspart, Novo Nordisk concludes that there is no need for additional pharmacovigilance activities beyond the planned routine pharmacovigilance activities.

Special pharmacovigilance agreement regarding NovoRapid® PumpCart®

NovoRapid® PumpCart® has been developed by Novo Nordisk for use with the Roche Diabetes Care Accu-Chek® Insight insulin pump and the Ypsomed AG YpsoPump® insulin pump. Novo Nordisk has entered a contractual collaboration agreement with both Roche Diabetes Care and Ypsomed AG for the exchange of the safety information and technical complaints information on NovoRapid® PumpCart® and the respective insulin pump (Accu-Chek® Insight insulin pump and YpsoPump® insulin pump), which also includes appendices outlining the responsibilities of pharmacovigilance activities ("Safety Data Exchange Arrangement [SDEA]" and "Technical Complaint Handling Arrangement").

Novo Nordisk has the full responsibility for safety surveillance, labelling, any aggregated reports, RMPs, single case reporting and the global database for NovoRapid® PumpCart®. Roche Diabetes

Care and Ypsomed AG are responsible for reporting any received AEs or technical complaint concerning NovoRapid® PumpCart® or the combined system (NovoRapid® PumpCart® combined with the Accu-Chek® Insight insulin pump and YpsoPump® insulin pump, respectively) within agreed timelines to Novo Nordisk in order for Novo Nordisk to be in compliance with regulatory requirements as marketing authorisation holder (MAH) for NovoRapid® PumpCart®.

Likewise, Roche Diabetes Care and Ypsomed AG are responsible for being in compliance with any regulatory requirements in connection to the Accu-Chek® Insight insulin pump and YpsoPump® insulin pump, respectively. Novo Nordisk is obligated to forward information on AEs or technical complaints related to the respective insulin pump or the combined system to Roche Diabetes Care or Ypsomed AG within a specified timeline.

Overall, Roche Diabetes Care and Ypsomed AG are responsible for AEs and technical complaints related to the combined system with the respective insulin pump. This includes coordination of any necessary investigation by one of the parties. However, Novo Nordisk will perform any investigation on NovoRapid® PumpCart® and provide a report to Roche Diabetes Care and Ypsomed AG to be included in the full investigation of the combined system. At the end of an investigation, Novo Nordisk will receive a summary report from Roche Diabetes Care of the full investigation, including the root cause of the complaint.

Novo Nordisk is responsible for conducting follow-up on NovoRapid® PumpCart®. Roche Diabetes Care is responsible for conducting follow-up on the Accu-Chek® Insight insulin pump and the combined system. Likewise, Ypsomed AG is responsible for conducting follow-up on the YpsoPump® insulin pump and the combined system. If permission for follow-up is restricted by the reporter to the part receiving the initial information, the receiving part is obligated to forward all follow-up questions to the reporter of the information on behalf of the other part.

Novo Nordisk and Roche Diabetes Care/Ypsomed AG are obliged to immediately inform the other about any risks which may negatively affect the benefit–risk profile, have consequences with regard to information about the use of the combined system or may require urgent safety measures.

3.1 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

3.1.1 Specific adverse reaction follow-up questionnaires

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

3.1.2 Other forms of routine pharmacovigilance activities

No other forms of routine pharmacovigilance activities are proposed.

3.2 Additional pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance studies/activities with insulin aspart under categories 1-3 (imposed, specific obligations and required activities) in the pharmacovigilance plan for insulin aspart until the DLP of this RMP. Routine pharmacovigilance of adverse events is considered sufficient to monitor and analyse the safety concerns associated with insulin aspart.

Novo Nordisk has entered a contractual collaboration agreement with both Roche Diabetes Care and Ypsomed AG for the exchange of the safety information and technical complaints information on NovoRapid® PumpCart® and the respective insulin pump (Accu-Chek® Insight insulin pump and YpsoPump® insulin pump), as described in detail in Section 3.

3.3 Summary table of additional pharmacovigilance activities

There are no additional pharmacovigilance activities/studies ongoing or planned for insulin aspart.

4 Plans for post-authorisation efficacy studies

There are no imposed post-authorisation efficacy studies ongoing or planned for insulin aspart.

5 Risk minimisation measures

5.1 Routine risk minimisation measures

The safety concerns associated with insulin aspart are considered to be fully characterised and appropriately managed through labelling. No further actions are deemed necessary.

5.2 Additional risk minimisation measures

No additional risk minimisation measures are planned for insulin aspart.

6 Summary of the risk management plan for insulin aspart

6.1 Summary of the risk management plan for NovoRapid® (insulin aspart)

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

SmPC and PL of NovoRapid® give essential information to HCPs and patients on how NovoRapid® should be used.

This summary of the RMP for NovoRapid® 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 European public assessment reports (EPAR).

Important new concerns or changes to the current ones will be included in updates of RMP for NovoRapid®.

6.1.1 The medicine and what it is used for

NovoRapid® is authorised for treatment of diabetes mellitus (see SmPC for the full indication). It contains insulin aspart as the active substance. NovoRapid® is administered by subcutaneous injection. NovoRapid® can also be used for CSII and can be given intravenously by HCPs.

Further information about the evaluation of benefits of NovoRapid® can be found in EPAR for NovoRapid®, including in its plain-language summary, available on the EMA website, under the medicine's webpage *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000258/human_med_000935.jsp&mid=WC0b01ac058001d124.*

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

Important risks of NovoRapid®, together with measures to minimise such risks and the proposed studies for learning more about risks of NovoRapid®, 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 PL and SmPC addressed to patients and HCPs
- 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 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*.

6.1.2.1 List of important risks and missing information

Important risks of NovoRapid® 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 NovoRapid®. 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). An overview of important risks and missing information for NovoRapid® is provided in Table 6-1.

Table 6-1 Important risks and missing information, NovoRapid®

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

6.1.2.2 Summary of important risks

The important risks are well described in the proposed product information and appropriately managed by routine pharmacovigilance activities and risk minimisation measures already in place.

6.1.2.3 Post-authorisation development plan

This section is not applicable as there are no imposed post-authorisation efficacy studies ongoing or planned for NovoRapid®.

6.2 Summary of the risk management plan for NovoMix® (insulin aspart)

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

SmPC and PL of NovoMix® give essential information to HCPs and patients on how NovoMix® should be used.

This summary of the RMP for NovoMix® 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 RMP for NovoMix®.

6.2.1 The medicine and what it is used for

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

Further information about the evaluation of benefits of NovoMix® can be found in EPAR for NovoMix®, including in its plain-language summary, available on the EMA website, under the medicine's webpage *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000308/human_med_000933.jsp&mid=WC0b01ac058001d124.*

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

Important risks of NovoMix®, together with measures to minimise such risks and the proposed studies for learning more about risks of NovoMix®, 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 PL and SmPC addressed to patients and HCPs
- 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 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*.

6.2.2.1 List of important risks and missing information

Important risks of NovoMix® 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 NovoMix®. 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). An overview of important risks and missing information for NovoMix® is provided in Table 6-2.

Table 6-2 Important risks and missing information, NovoMix®

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

6.2.2.2 Summary of important risks

The important risks are well described in the proposed product information and appropriately managed by routine pharmacovigilance activities and risk minimisation measures already in place.

6.2.2.3 Post-authorisation development plan

This section is not applicable as there are no imposed post-authorisation efficacy studies ongoing or planned for NovoMix®.

Risk Management Plan

Insulin aspart

Annex 4 - Specific adverse event follow-up forms

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

Risk Management Plan

Insulin aspart

Annex 6 - Details of proposed additional risk minimisation measures

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