

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ryzodeg 100 units/mL solution for injection in pre-filled pen
Ryzodeg 100 units/mL solution for injection in cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution contains 100 units insulin degludec/insulin aspart* in the ratio 70/30 (equivalent to 2.56 mg insulin degludec and 1.05 mg insulin aspart).

Ryzodeg 100 units/mL solution for injection in pre-filled pen

One pre-filled pen contains 300 units of insulin degludec/insulin aspart in 3 mL solution.

Ryzodeg 100 units/mL solution for injection in cartridge

One cartridge contains 300 units of insulin degludec/insulin aspart in 3 mL solution.

*Produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ryzodeg 100 units/mL solution for injection in pre-filled pen

Solution for injection (FlexTouch).

Ryzodeg 100 units/mL solution for injection in cartridge

Solution for injection (Penfill).

Clear, colourless, neutral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children from the age of 2 years.

4.2 Posology and method of administration

Posology

This medicinal product is a soluble insulin product consisting of the basal insulin degludec and the rapid-acting prandial insulin aspart.

Ryzodeg can be administered once or twice daily with the main meal(s). When needed, the patient can change the time of administration as long as this medicinal product is dosed with the largest meal when taken once daily.

The potency of insulin analogues, including Ryzodeg, is expressed in units. One (1) unit of this insulin corresponds to 1 international unit of human insulin, 1 unit of insulin glargine, 1 unit of insulin detemir or 1 unit of biphasic insulin aspart.

In patients with type 2 diabetes mellitus, this insulin can be administered alone, in combination with oral antidiabetic medicinal products, and in combination with bolus insulin (see section 5.1).

In type 1 diabetes mellitus, Ryzodeg is combined with short-/rapid-acting insulin at the remaining

meals.

Ryzodeg is to be dosed in accordance with the individual patient's needs. Dose-adjustments are recommended to be primarily based on fasting plasma glucose measurements.

Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Flexibility in dosing time

Ryzodeg allows for flexibility in the timing of insulin administration as long as it is dosed with the main meal(s).

If a dose of this medicinal product is missed, the patient can take the missed dose with the next main meal of that day and thereafter resume the usual dosing schedule. Patients should not take an extra dose to make up for a missed dose.

Initiation

Patients with type 2 diabetes mellitus

The recommended total daily starting dose is 10 units with meal(s) followed by individual dosage adjustments.

Patients with type 1 diabetes mellitus

The recommended starting dose of Ryzodeg is 60–70% of the total daily insulin requirements.

This medicinal product is to be used once daily at mealtime in combination with short-/rapid-acting insulin at the remaining meals followed by individual dosage adjustments.

Transfer from other insulin medicinal products

Close glucose monitoring is recommended during the transfer and in the following weeks. Doses and timing of concurrent rapid-acting or short-acting insulin products or other concomitant antidiabetic treatment may need to be adjusted.

Patients with type 2 diabetes mellitus

Patients switching from once-daily basal or premix insulin therapy can be converted unit-to-unit to once-daily Ryzodeg at the same total insulin dose as the patient's previous total daily insulin dose.

Patients switching from more than once-daily basal or premix insulin therapy can be converted unit-to-unit to twice-daily Ryzodeg at the same total insulin dose as the patient's previous total daily insulin dose.

Patients switching from basal/bolus insulin therapy to Ryzodeg will need to convert their dose based on individual needs. In general, patients are initiated on the same number of basal units.

Patients with type 1 diabetes mellitus

The recommended starting dose of Ryzodeg is 60–70% of the total daily insulin requirements in combination with short-/rapid-acting insulin at the remaining meals followed by individual dosage adjustments.

Special populations

Elderly (≥ 65 years old)

Ryzodeg can be used in the elderly. Glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis (see section 5.2).

Renal and hepatic impairment

Ryzodeg can be used in renal and hepatic impaired patients. Glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis (see section 5.2).

Paediatric population

There is no clinical experience with the use of this medicinal product in children below the age of 2 years.

This medicinal product can be used in adolescents and children from the age of 2 years (see section 5.1). When changing from another insulin regimen to Ryzodeg, dose reduction of total insulin needs to be considered on an individual basis in order to minimise the risk of hypoglycaemia (see section 4.4).

Ryzodeg should be used with special caution in children 2 to 5 years old because data from the clinical trial indicate that there may be a higher risk for severe hypoglycaemia in children in this age group (see sections 4.4, 4.8 and 5.1).

Method of administration

Subcutaneous use only.

This medicinal product must not be administered intravenously as it may result in severe hypoglycaemia.

This medicinal product must not be administered intramuscularly as it may change the absorption.

This medicinal product must not be used in insulin infusion pumps.

This medicinal product must not be drawn from the cartridge of the pre-filled pen into a syringe (see section 4.4).

Ryzodeg is administered subcutaneously by injection in the abdominal wall, the upper arm or the thigh. Injection sites are always to be rotated within the same region in order to reduce the risk of lipodystrophy.

Patients should be instructed to always use a new needle. The re-use of insulin pen needles increases the risk of blocked needles, which may cause under- or overdosing. In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet (see section 6.6).

Ryzodeg 100 units/mL solution for injection in pre-filled pen

Ryzodeg comes in a pre-filled pen (FlexTouch) designed to be used with NovoFine or NovoTwist injection needles. The pre-filled pen delivers 1–80 units in steps of 1 unit.

Ryzodeg 100 units/mL solution for injection in cartridge

Ryzodeg comes in a cartridge (Penfill) designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist injection needles.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypoglycaemia

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.5, 4.8 and 4.9).

In children, extra care should be taken to match insulin doses with food intake and physical activities in order to minimise the risk of hypoglycaemia. Ryzodeg may be associated with higher occurrence of severe hypoglycaemia compared to a basal-bolus regimen in the paediatric population, particularly in children 2 to 5 years old (see section 5.1). For this age group, Ryzodeg should be considered on an individual basis.

Patients whose blood glucose control is greatly improved (e.g. by intensified insulin therapy) may experience a change in their usual warning symptoms of hypoglycaemia and must be advised accordingly. Usual warning symptoms may disappear in patients with long-standing diabetes.

Concomitant illness, especially infections and fever, usually increases the patient's insulin requirement. Concomitant diseases in the kidney, liver or diseases affecting the adrenal, pituitary or thyroid gland may require changes in the insulin dose.

As with other basal insulin products or insulin products with a basal component, the prolonged effect of Ryzodeg may delay recovery from hypoglycaemia.

Hyperglycaemia

Administration of rapid-acting insulin is recommended in situations with severe hyperglycaemia.

Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Furthermore, concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement.

Usually, the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, and loss of appetite as well as acetone odour of breath. In type 1 diabetes mellitus, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Transfer from other insulin medicinal products

Transferring a patient to another type, brand or manufacturer of insulin must be done under medical supervision and may result in the need for a change in dosage.

Combination of pioglitazone and insulin medicinal products

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac failure. This should be kept in mind if treatment with the combination of pioglitazone and Ryzodeg is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Eye disorder

Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Avoidance of accidental mix-ups

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between Ryzodeg and other insulin products.

Patients must visually verify the dialled units on the dose counter of the pen. Therefore, the requirement for patients to self-inject is that they can read the dose counter on the pen. Patients who are blind or have poor vision must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device.

To avoid dosing errors and potential overdose, patients and healthcare professionals should never use a syringe to draw the medicinal product from the cartridge in the pre-filled pen.

In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet (see section 6.6).

Insulin antibodies

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with glucose metabolism.

The following substances may reduce the insulin requirement

Oral antidiabetic medicinal products, GLP-1 receptor agonists, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulfonamides.

The following substances may increase the insulin requirement

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no clinical experience with the use of this medicinal product in pregnant women.

Animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity.

In general, intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually decrease in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements usually return rapidly to pre-pregnancy values.

Breast-feeding

There is no clinical experience with Ryzodeg during breast-feeding. In rats, insulin degludec was secreted in milk; the concentration in milk was lower than in plasma.

It is unknown whether insulin degludec/insulin aspart is excreted in human milk. No metabolic effects are anticipated in the breast-fed newborn/infant.

Fertility

Animal reproduction studies with insulin degludec have not revealed any adverse effects on fertility.

4.7 Effects on ability to drive and use machines

This medicinal product has no or negligible influence on the ability to drive and use machines. However, the patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients must be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia (see section 'Description of selected adverse reactions' below).

Tabulated list of adverse reactions

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA System Organ Class. Frequency categories are defined according to the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reaction
Immune system disorders	Rare	Hypersensitivity Urticaria
Metabolism and nutrition disorders	Very common	Hypoglycaemia
Skin and subcutaneous tissue disorders	Not known	Lipodystrophy
General disorders and administration site conditions	Common	Injection site reactions
	Uncommon	Peripheral oedema

Description of selected adverse reactions

Immune system disorders

With insulin preparations, allergic reactions may occur. Immediate-type allergic reactions to either insulin itself or the excipients may potentially be life-threatening.

With Ryzodeg, hypersensitivity (manifested with swelling of tongue and lips, diarrhoea, nausea, tiredness and itching) and urticaria were reported rarely.

Hypoglycaemia

Hypoglycaemia 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. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

Lipodystrophy

Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

Injection site reactions

Injection site reactions (including injection site haematoma, pain, haemorrhage, erythema, nodules, swelling, discolouration, pruritus, warmth and injection site mass) occurred in patients treated with Ryzodeg. These reactions are usually mild and transitory and they normally disappear during continued treatment.

Paediatric population

Ryzodeg has been administered to children and adolescents up to 18 years of age for the investigation of pharmacokinetic properties (see section 5.2). Safety and efficacy have been demonstrated in a trial in children aged 2 to less than 18 years. The frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population with the exception of a signal of higher occurrence of severe hypoglycaemia compared to a basal-bolus regimen in the paediatric population, particularly in children 2 to 5 years old (see section 4.2, 4.4 and 5.1).

Other special populations

Based on results from clinical trials, the frequency, type and severity of adverse reactions observed in the elderly and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

A specific overdose for insulin cannot be defined. However, hypoglycaemia may develop over sequential stages if a patient is dosed with more insulin than required:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or other products containing sugar. It is therefore recommended that the patient always carries glucose-containing products.
- Severe hypoglycaemic episodes, where the patient is not able to treat himself, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting, ATC code: A10AD06.

Mechanism of action

Insulin degludec and insulin aspart bind specifically to the human insulin receptor and result in the same pharmacological effects as human insulin.

The blood glucose-lowering effect of insulin is due to the facilitated uptake of glucose following the binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

Pharmacodynamic effects

The pharmacodynamic effect of Ryzodeg is distinctively separated for the two components (Figure 1), and the resulting action profile reflects the individual components, the rapid-acting insulin aspart and the basal component insulin degludec.

The basal component of Ryzodeg (insulin degludec) forms soluble multi-hexamers upon subcutaneous injection, resulting in a depot from which insulin degludec is continuously and slowly absorbed into the circulation leading to a flat and stable glucose-lowering effect. This effect is maintained in the co-formulation with insulin aspart and does not interfere with the rapid-acting insulin aspart monomers.

Ryzodeg has a rapid onset of action occurring soon after injection providing mealtime coverage while the basal component has a flat and stable action profile providing continuous coverage of the basal insulin requirements. The duration of action of a single-dose of Ryzodeg is beyond 24 hours.

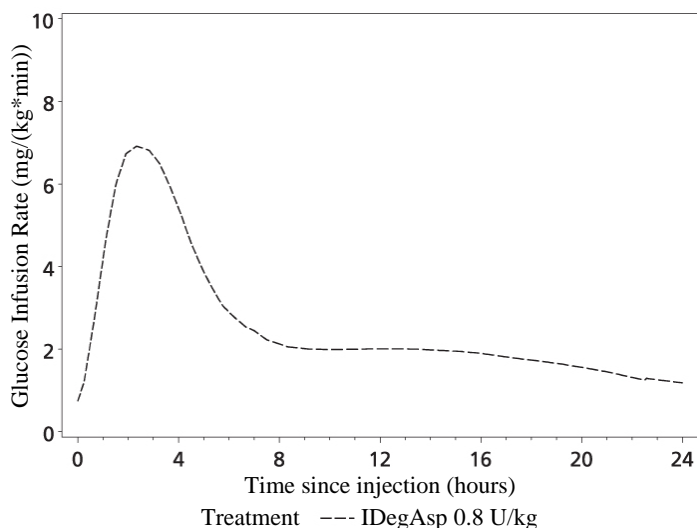


Figure 1: Pharmacodynamics, single dose – Mean glucose infusion rate profile – Patients with type 1 diabetes – 0.8 U/kg Ryzodeg – Trial 3539

The total and maximum glucose-lowering effects of Ryzodeg increase linearly with increasing doses. Steady state will occur after 2–3 days of dose administration.

There is no difference in the pharmacodynamic effect of this medicinal product between elderly and younger patients.

Clinical efficacy and safety

Five multinational, randomised, controlled, open-label, treat-to-target clinical studies of 26 weeks' and 52 weeks' duration were conducted exposing a total of 1,360 patients with diabetes mellitus (362 patients in type 1 diabetes mellitus and 998 patients in type 2 diabetes mellitus) to Ryzodeg. Ryzodeg administered once daily (o.d.) plus Oral Antidiabetic Drugs (OADs) was compared to insulin glargine (IGlar) (o.d.) plus OADs in two trials in type 2 diabetes mellitus (Table 1). Ryzodeg b.i.d. plus OADs was compared to biphasic insulin aspart 30 (BIAsp 30) b.i.d. plus OADs in two trials in type 2 diabetes mellitus (Table 2). Ryzodeg o.d. plus insulin aspart (IAsp) was also compared to once-daily (o.d.) or twice-daily insulin detemir (IDet) plus IAsp in type 1 diabetes mellitus (Table 3).

Non-inferiority in HbA_{1c} change from baseline to end-of-trial was confirmed in all studies against all comparators when treating patients to target.

In two trials combining insulin and OAD treatment in both insulin-naïve (insulin initiation) and insulin-using (insulin intensification) patients with type 2 diabetes mellitus, Ryzodeg o.d. demonstrated similar glycaemic control (HbA_{1c}) compared to IGlar (administered according to label) (Table 1). As Ryzodeg contains a rapid-acting mealtime insulin (insulin aspart), prandial glycaemic control at the dosing meal is improved relative to administering basal insulin only; see trial results in Table 1. A lower rate of nocturnal hypoglycaemia (defined as episodes between midnight and 6 a.m. confirmed by plasma glucose < 3.1 mmol/l or by patient needing third party assistance) was observed with Ryzodeg relative to IGlar (Table 1).

Ryzodeg b.i.d. demonstrated similar glycaemic control (HbA_{1c}) compared with BIAsp 30 b.i.d. in patients with type 2 diabetes mellitus. It demonstrates superior improvements in fasting plasma glucose levels compared to patients treated with BIAsp 30. Ryzodeg causes a lower rate of overall and nocturnal hypoglycaemia (Table 2).

In patients with type 1 diabetes mellitus, treatment with Ryzodeg o.d. plus IAsp for the remaining meals demonstrated similar glycaemic control (HbA_{1c} and fasting plasma glucose) with a lower rate of nocturnal hypoglycaemia compared to a basal/bolus regimen with IDet plus IAsp at all meals (Table 3).

There is no clinically relevant development of insulin antibodies after long-term treatment of Ryzodeg.

Table 1 Result from two 26-weeks' trials in type 2 diabetes mellitus with Ryzodeg given once daily

	Ryzodeg (o.d.)¹ Insulin naïve	IGlar (o.d.)¹ Insulin naïve	Ryzodeg (o.d.)² Insulin users	IGlar (o.d.)² Insulin users
N	266	263	230	233
Mean HbA1c (%)				
End of trial	7.2	7.2	7.3	7.4
Mean change	-1.65	-1.72	-0.98	-1.00
	<i>Difference: 0.03 [-0.14;0.20]</i>		<i>Difference: -0.03 [-0.20;0.14]</i>	
Fasting Plasma Glucose (FPG) (mmol/l)				
End of trial	6.8	6.3	6.3	6.0
Mean change	-3.32	-4.02	-1.68	-1.88
	<i>Difference: 0.51 [0.09;0.93]</i>		<i>Difference: 0.33 [-0.11;0.77]</i>	
Prandial Blood glucose Increment 90 minutes after dosing meal (Plasma) (mmol/l)				
End of trial	1.9	3.4	1.2	2.6
Mean change	-1.5	-0.3	-1.5	-0.6
Hypoglycaemia Rate (per patient year of exposure)				
Severe	0.01	0.01	0.00	0.04
Confirmed ³	4.23	1.85	4.31	3.20
	<i>Ratio: 2.17 [1.59;2.94]</i>		<i>Ratio: 1.43 [1.07;1.92]</i>	
Nocturnal confirmed ³	0.19	0.46	0.82	1.01
	<i>Ratio: 0.29 [0.13;0.65]</i>		<i>Ratio: 0.80 [0.49;1.30]</i>	

¹ Once-daily regimen + Metformin

² Once-daily regimen + Metformin ± pioglitazone ± DPP-4 inhibitor

³ Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose < 3.1 mmol/L or by the patient needing third party assistance. Nocturnal confirmed hypoglycaemia was defined as episodes between midnight and 6 a.m.

Table 2 Result from two 26-weeks' trials in type 2 diabetes mellitus with Ryzodeg given twice daily

	Ryzodeg (b.i.d.)¹ Insulin users	BIAsp 30 (b.i.d.)¹ Insulin users	Ryzodeg (b.i.d.)² Insulin users	BIAsp 30 (b.i.d.)² Insulin users
N	224	222	280	142
Mean HbA1c (%)				
End of trial	7.1	7.1	7.1	7.0
Mean change	-1.28	-1.30	-1.38	-1.42
	<i>Difference: -0.03 [-0.18;0.13]</i>		<i>Difference: 0.05 [-0.10;0.20]</i>	
FPG (mmol/l)				
End of trial	5.8	6.8	5.4	6.5
Mean change	-3.09	-1.76	-2.55	-1.47
	<i>Difference: -1.14 [-1.53;-0.76]</i>		<i>Difference: -1.06 [-1.43;-0.70]</i>	
Hypoglycaemia Rate (per patient year of exposure)				
Severe	0.09	0.25	0.05	0.03
Confirmed ³	9.72	13.96	9.56	9.52
	<i>Ratio: 0.68 [0.52;0.89]</i>		<i>Ratio: 1.00 [0.76;1.32]</i>	
Nocturnal confirmed ³	0.74	2.53	1.11	1.55
	<i>Ratio: 0.27 [0.18;0.41]</i>		<i>Ratio: 0.67 [0.43;1.06]</i>	

¹ Twice-daily regimen ± metformin ± pioglitazone ± DPP-4 inhibitor

² Twice-daily regimen ± metformin

³ Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose < 3.1 mmol/L or by the patient needing third party assistance. Nocturnal confirmed hypoglycaemia was defined as episodes between midnight and 6 a.m.

Table 3 Result of a 26-weeks' trial in type 1 diabetes mellitus

	Ryzodeg (o.d.)¹	IDet (o.d./b.i.d.)²
N	366	182
Mean HbA1c (%)		
End of trial	7.6	7.6
Mean change	-0.73	-0.68
	<i>Difference: -0.05 [-0.18;0.08]</i>	
FPG (mmol/l)		
End of trial	8.7	8.6
Mean change	-1.61	-2.41
	<i>Difference: 0.23 [-0.46;0.91]</i>	
Hypoglycaemia Rate (per patient year of exposure)		
Severe	0.33	0.42
Confirmed ³	39.2	44.3
	<i>Ratio: 0.91 [0.76;1.09]</i>	
Nocturnal confirmed ³	3.71	5.72
	<i>Ratio: 0.63 [0.49;0.81]</i>	

¹ Once-daily regimen + insulin aspart to cover mealtime insulin requirements

² Once- or twice-daily regimen + insulin aspart to cover mealtime insulin requirements

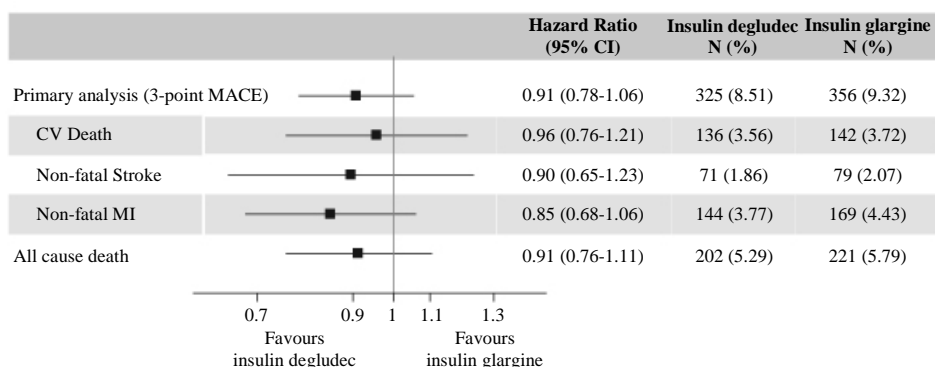
³ Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose < 3.1 mmol/L or by the patient needing third party assistance. Nocturnal confirmed hypoglycaemia was defined as episodes between midnight and 6 a.m.

Cardiovascular safety

DEVOTE was a randomised, double-blind, and event-driven clinical trial focusing on insulin degludec, the long-acting component of Ryzodeg. The trial had a median duration of 2 years and compared the cardiovascular safety of insulin degludec vs insulin glargine (100 units/mL) in 7,637 patients with type 2 diabetes mellitus at high risk of cardiovascular events.

The primary analysis was time from randomisation to first occurrence of a 3-component major adverse cardiovascular event (MACE) defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The trial was designed as a non-inferiority trial to exclude a pre-specified risk margin of 1.3 for the hazard ratio (HR) of MACE comparing insulin degludec to insulin glargine. The cardiovascular safety of insulin degludec as compared to insulin glargine was confirmed (HR 0.91 [0.78; 1.06]) (Figure 2).

Results from subgroup analyses (e.g. sex, diabetes duration, CV risk group and previous insulin regimen) were aligned with the primary analysis. At baseline, HbA_{1c} was 8.4% in both treatment groups and after 2 years HbA_{1c} was 7.5% both with insulin degludec and insulin glargine.



N: Number of subjects with a first EAC confirmed event during trial. %: Percentage of subjects with a first EAC confirmed event relative to the number of randomised subjects. EAC: Event adjudication committee. CV: Cardiovascular. MI: Myocardial infarction. CI: 95% confidence interval.

Figure 2 Forest plot of analysis of the composite 3-point MACE and individual cardiovascular endpoints in DEVOTE

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of trials with Ryzodeg in:

- Neonates and infants from birth to less than 12 months of age with type 1 diabetes mellitus.
- In all subsets of the paediatric population in type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

The efficacy and safety of Ryzodeg have been studied in a randomised controlled clinical trial in children and adolescents with diabetes mellitus type 1 for a period of 16 weeks (n=362). Patients in the Ryzodeg arm included 40 exposed children aged 2–5 years, 61 children aged 6–11 years and 80 adolescents aged 12–17 years. Ryzodeg dosed once daily with the main meal plus insulin aspart for the remaining meals showed similar reduction in HbA_{1c} at week 16 and no differences in FPG and SMPG compared to comparator insulin detemir dosed once or twice daily plus mealtime insulin aspart. At week 16, the mean total daily insulin dose was 0.88 vs 1.01 units/kg in the Ryzodeg and insulin detemir arms, respectively. The rates (events per patient-year of exposure) of confirmed hypoglycaemia (ISPAD 2009 definition: 46.23 vs 49.55) and nocturnal confirmed hypoglycaemia (5.77 vs 5.40) were comparable with Ryzodeg vs insulin detemir whereas the rate of severe hypoglycaemia (0.26 vs 0.07) was higher in the Ryzodeg arm although the difference was not statistically significant. Few severe hypoglycaemic episodes were reported in each group; the observed rate of severe hypoglycaemia within the Ryzodeg arm was higher for subjects aged 2–5 years compared to subjects aged 6–11 years or 12–17 years (0.42 vs 0.21 and 0.21 respectively). An efficacy and safety evaluation for adolescent patients with type 2 diabetes mellitus has been made using data from adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. This assessment supports the use of Ryzodeg in adolescent patients with type 2 diabetes mellitus.

5.2 Pharmacokinetic properties

Absorption

After subcutaneous injection, soluble and stable multi-hexamers of insulin degludec are formed creating a depot of insulin in the subcutaneous tissue, while not interfering with the rapid release of insulin aspart monomers into the circulation. Insulin degludec monomers gradually separate from the multi-hexamers thus resulting in a slow and continuous delivery of insulin degludec into the circulation. Steady-state serum concentration of the basal component (insulin degludec) is reached after 2–3 days of daily Ryzodeg administration.

The rapid absorption characteristics of the well-established insulin aspart are maintained by Ryzodeg. The pharmacokinetic profile for insulin aspart appears 14 minutes after injection with a peak concentration after 72 minutes.

Distribution

The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. Insulin aspart has a low binding to plasma proteins (<10%), similar to that seen with regular human insulin.

Biotransformation

Degradation of insulin degludec and insulin aspart is similar to that of human insulin; all metabolites formed are inactive.

Elimination

The half-life after subcutaneous administration of Ryzodeg is determined by the rate of absorption from the subcutaneous tissue. The half-life of the basal component (insulin degludec) at steady state is 25 hours independent of dose.

Linearity

Total exposure with Ryzodeg increases proportionally with increasing dose of the basal component (insulin degludec) and the mealtime component (insulin aspart) in type 1 and type 2 diabetes mellitus.

Gender

There is no gender difference in the pharmacokinetic properties of Ryzodeg.

Elderly, race, renal and hepatic impairment

There are no clinically relevant differences in the pharmacokinetics of Ryzodeg between elderly and younger adult patients, between races or between healthy subjects and patients with renal or hepatic impairment.

Paediatric population

The pharmacokinetic properties of Ryzodeg in type 1 diabetes mellitus were investigated in children (6–11 years) and adolescents (12–18 years) and compared to adults after single dose administration. The steady-state pharmacokinetic properties of the insulin degludec component of Ryzodeg were investigated using a population pharmacokinetic analysis in children down to 1 year of age.

Total exposure and peak concentration of insulin aspart were higher in children than in adults and were similar for adolescents and adults.

The pharmacokinetic properties of insulin degludec in children (1–11 years) and adolescents (12–18 years) were at steady state comparable to those observed in adults with type 1 diabetes mellitus.

Total exposure of insulin degludec after single dose administration was, however, higher in children and adolescents than in adults with type 1 diabetes mellitus.

5.3 Preclinical safety data

Non-clinical data reveal no safety concerns for humans based on studies of safety pharmacology, repeated dose toxicity, carcinogenic potential, and toxicity to reproduction.

The ratio of mitogenic relative to metabolic potency for insulin degludec is comparable to that of human insulin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol

Metacresol

Phenol

Sodium chloride

Zinc acetate

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Substances added to Ryzodeg may cause degradation of insulin degludec and/or insulin aspart.

Ryzodeg must not be added to infusion fluids.

6.3 Shelf life

30 months.

Ryzodeg 100 units/mL solution for injection in pre-filled pen

After first opening or carried as a spare, the medicinal product may be stored for a maximum of 4 weeks. Do not store above 30°C. Can be stored in a refrigerator (2°C – 8°C). Keep the cap on the pen in order to protect from light.

Ryzodeg 100 units/mL solution for injection in cartridge

After first opening or carried as a spare, the medicinal product may be stored for a maximum of 4 weeks. Do not store above 30°C. Do not refrigerate. Keep the cartridges in the outer carton in order to protect from light.

6.4 Special precautions for storage

Ryzodeg 100 units/mL solution for injection in pre-filled pen

Before first use: Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep away from the freezing element.

Keep the cap on the pen in order to protect from light.

Ryzodeg 100 units/mL solution for injection in cartridge

Before first use:

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep away from the freezing element.

Keep the cartridges in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Ryzodeg 100 units/mL solution for injection in pre-filled pen

3 mL solution in a cartridge (type 1 glass) with a plunger (halobutyl) and a laminate rubber sheet (halobutyl/polyisoprene) contained in a multidose disposable pre-filled pen made of polypropylene.

Pack sizes of 1 (with or without needles), 5 (without needles) and multipack containing 10 (2 packs of 5) (without needles) pre-filled pens.

Not all pack sizes may be marketed.

Ryzodeg 100 units/mL solution for injection in cartridge

3 mL solution in a cartridge (type 1 glass) with a plunger (halobutyl) and a laminate rubber sheet (halobutyl/polyisoprene) in a carton.

Pack sizes of 5 and 10 cartridges.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is for use by one person only. It must not be refilled.

Ryzodeg must not be used if the solution does not appear clear and colourless.

Ryzodeg which has been frozen must not be used.

A new needle must always be attached before each use. Needles must not be re-used. The patient should discard the needle after each injection.

In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet.

Any waste material should be disposed of in accordance with local requirements.

For detailed instructions for use, see the package leaflet.

Ryzodeg 100 units/mL solution for injection in pre-filled pen

The pre-filled pen (FlexTouch) is designed to be used with NovoFine/NovoTwist injection needles up to a length of 8 mm. It delivers 1–80 units in steps of 1 unit. Detailed instructions accompanying the pre-filled pen must be followed.

Ryzodeg 100 units/mL solution for injection in cartridge

The cartridge (Penfill) is designed to be used with Novo Nordisk delivery systems (durable devices for repeated use not included in the pack) and NovoFine/NovoTwist injection needles up to a length of 8 mm. Detailed instructions accompanying the delivery system must be followed.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBERS

Ryzodeg 100 units/mL solution for injection in pre-filled pen

EU/1/12/806/001
EU/1/12/806/002
EU/1/12/806/003
EU/1/12/806/004
EU/1/12/806/005

Ryzodeg 100 units/mL solution for injection in cartridge

EU/1/12/806/007
EU/1/12/806/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 January 2013

Date of latest renewal: 21 September 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances

Novo Nordisk A/S
Hallas Allé
DK-4400 Kalundborg
Denmark

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

Name and address of the manufacturer responsible for batch release

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports (PSUR)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (100 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT

Ryzodeg 100 units/mL solution for injection in pre-filled pen
70% insulin degludec / 30% insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCES

One pre-filled pen contains 300 units of insulin degludec/insulin aspart in 3 mL solution
1 mL solution contains 100 units of insulin degludec/insulin aspart in the ratio 70/30 (equivalent to 2.56 mg insulin degludec and 1.05 mg insulin aspart)

3. LIST OF EXCIPIENTS

Glycerol, metacresol, phenol, sodium chloride, zinc acetate, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (FlexTouch)

1 x 3 mL

1 x 3 mL + 7 NovoFine needles

1 x 3 mL + 7 NovoTwist needles

5 x 3 mL

5. METHOD AND ROUTE OF ADMINISTRATION

Needles are not included

Read the package leaflet before use.

Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use only clear, colourless solution

Single patient use only

Do not withdraw solution from the pen

8. EXPIRY DATE

EXP

After first opening: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)

Do not freeze

After first opening: Can be stored in a refrigerator (2°C – 8°C). Do not store above 30°C. Keep the cap on the pen in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle safely after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/12/806/001 1 pen of 3 mL
EU/1/12/806/002 1 pen of 3 mL and 7 NovoFine needles
EU/1/12/806/003 1 pen of 3 mL and 7 NovoTwist needles
EU/1/12/806/004 5 pens of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Ryzodeg pre-filled pen 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (100 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Ryzodeg 100 units/mL solution for injection
70% insulin degludec / 30% insulin aspart
FlexTouch

2. METHOD OF ADMINISTRATION

SC use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mL

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACK LABEL (100 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT

Ryzodeg 100 units/mL solution for injection in pre-filled pen
70% insulin degludec / 30% insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCES

One pre-filled pen contains 300 units of insulin degludec/insulin aspart in 3 mL solution
1 mL solution contains 100 units of insulin degludec/insulin aspart in the ration of 70/30 (equivalent to 2.56 mg insulin degludec and 1.05 mg insulin aspart)

3. LIST OF EXCIPIENTS

Glycerol, metacresol, phenol, sodium chloride, zinc acetate, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (FlexTouch)

Multipack: 10 (2 packs of 5) 3 mL pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only
Do not withdraw solution from the pen

8. EXPIRY DATE

EXP
After first opening: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)

Do not freeze

After first opening: Can be stored in a refrigerator (2°C – 8°C). Do not store above 30°C. Keep the cap on the pen in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle safely after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/12/806/005 10 pens of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Ryzodeg pre-filled pen 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE INNER PACKAGING

INNER CARTON FOR MULTIPACK (100 units/mL pre-filled pen (FlexTouch))

1. NAME OF THE MEDICINAL PRODUCT

Ryzodeg 100 units/mL solution for injection in pre-filled pen
70% insulin degludec / 30% insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCES

One pre-filled pen contains 300 units of insulin degludec/insulin aspart in 3 mL solution
1 mL solution contains 100 units of insulin degludec/insulin aspart in the ration of 70/30 (equivalent to 2.56 mg insulin degludec and 1.05 mg insulin aspart)

3. LIST OF EXCIPIENTS

Glycerol, metacresol, phenol, sodium chloride, zinc acetate, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (FlexTouch)

5 x 3 mL. Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only
Do not withdraw solution from the pen

8. EXPIRY DATE

EXP
After first opening: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)

Do not freeze

After first opening: Can be stored in a refrigerator (2°C – 8°C). Do not store above 30°C. Keep the cap on the pen in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle safely after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/12/806/005 10 pens of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Ryzodeg pre-filled pen 100

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (100 units/mL cartridge (Penfill))

1. NAME OF THE MEDICINAL PRODUCT

Ryzodeg 100 units/mL solution for injection in cartridge
70% insulin degludec / 30% insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCES

One cartridge contains 300 units of insulin degludec/insulin aspart in 3 mL solution
1 mL solution contains 100 units of insulin degludec/insulin aspart in the ratio of 70/30 (equivalent to 2.56 mg insulin degludec and 1.05 mg insulin aspart)

3. LIST OF EXCIPIENTS

Glycerol, metacresol, phenol, sodium chloride, zinc acetate, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (Penfill)

5 x 3 mL
10 x 3 mL

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only

8. EXPIRY DATE

EXP
After first opening: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)
Do not freeze

After first opening: Do not refrigerate. Do not store above 30°C. Keep the cartridge in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/12/806/007 5 cartridges of 3 mL
EU/1/12/806/008 10 cartridges of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Ryzodeg cartridge 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (100 units/mL cartridge (Penfill))

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Ryzodeg 100 units/mL solution for injection
70% insulin degludec / 30% insulin aspart
Penfill

2. METHOD OF ADMINISTRATION

SC use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mL

6. OTHER

Novo Nordisk A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ryzodeg 100 units/mL solution for injection in pre-filled pen 70% insulin degludec / 30% insulin aspart

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Ryzodeg is and what it is used for
2. What you need to know before you use Ryzodeg
3. How to use Ryzodeg
4. Possible side effects
5. How to store Ryzodeg
6. Contents of the pack and other information

1. What Ryzodeg is and what it is used for

Ryzodeg is used to treat diabetes mellitus in adults, adolescents and children from the age of 2 years. It helps your body reduce your blood sugar level.

This medicine contains two types of insulin:

- Basal insulin called insulin degludec, this has a long blood sugar-lowering effect.
- Rapid-acting insulin called insulin aspart, this lowers your blood sugar soon after you inject it.

2. What you need to know before you use Ryzodeg

Do not use Ryzodeg:

- if you are allergic to insulin degludec, insulin aspart or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Ryzodeg. Be especially aware of the following:

- Low blood sugar (hypoglycaemia) – if your blood sugar is too low, follow the guidance for low blood sugar in section 4.
- High blood sugar (hyperglycaemia) – if your blood sugar is too high, follow the guidance for high blood sugar in section 4.
- Switching from other insulin medicines – the insulin dose may need to be changed if you switch from another type, brand or manufacturer of insulin. Talk to your doctor.
- Pioglitazone used together with insulin, see ‘Pioglitazone’ below.
- Eye disorder – fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disorder. If you experience eye problems, talk to your doctor.
- Ensuring you use the right type of insulin – always check the insulin label before each injection to avoid accidentally confusing Ryzodeg with other insulin products.

If you have poor eyesight, please see section 3.

Children and adolescents

Ryzodeg can be used in adolescents and children from the age of 2 years with diabetes mellitus. Ryzodeg should be used with special caution in children 2 to 5 years old. The risk for very low blood sugar may be higher in this age group. There is no experience with the use of this medicine in children below the age of 2 years.

Other medicines and Ryzodeg

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. Some medicines affect your blood sugar level, this may mean your insulin dose has to be changed.

Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:

- other medicines for diabetes (oral and injectable)
- sulfonamides, for infections
- anabolic steroids, such as testosterone
- beta-blockers, for high blood pressure. They may make it harder to recognise the warning signs of too low blood sugar (see section 4 'Warning signs of too low blood sugar')
- acetylsalicylic acid (and other salicylates), for pain and mild fever
- monoamine oxidase (MAO) inhibitors, for depression
- angiotensin converting enzyme (ACE) inhibitors, for some heart problems or high blood pressure.

Your blood sugar level may rise (hyperglycaemia) if you take:

- danazol, for endometriosis
- oral contraceptives (birth control pills)
- thyroid hormones, for thyroid problems
- growth hormone, for growth hormone deficiency
- glucocorticoids such as 'cortisone', for inflammation
- sympathomimetics such as epinephrine (adrenaline), salbutamol or terbutaline, for asthma
- thiazides, for high blood pressure or if your body keeps too much water (water retention).

Octreotide and lanreotide: used to treat a rare condition involving too much growth hormone (acromegaly). They may increase or decrease your blood sugar level.

Pioglitazone: oral antidiabetic medicine used to treat type 2 diabetes mellitus. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor immediately if you experience signs of heart failure such as unusual shortness of breath, rapid increase in weight or localised swelling (oedema).

If any of the above applies to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Ryzodeg with alcohol

If you drink alcohol, your need for insulin may change. Your blood sugar level may either rise or fall. You should therefore monitor your blood sugar level more often than usual.

Pregnancy and breast-feeding

It is not known if Ryzodeg affects the baby in pregnancy or during breast-feeding. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes is needed in pregnancy. Avoiding too low blood sugar (hypoglycaemia) is particularly important for the health of your baby.

Driving and using machines

Having too low or too high blood sugar can affect your ability to drive or use any tools or machines. If your blood sugar is too low or too high, your ability to concentrate or react might be affected. This

could be dangerous to yourself or others. Ask your doctor whether you can drive if:

- you often get too low blood sugar
- you find it hard to recognise too low blood sugar.

Important information about some of the ingredients in Ryzodeg

This medicine contains less than 1 mmol sodium (23 mg) per dose. This means that the medicine is essentially 'sodium-free'.

3. How to use Ryzodeg

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use the pen without help. Get help from a person with good eyesight who is trained to use the FlexTouch pre-filled pen.

The pre-filled pen can provide a dose of 1–80 units in one injection in steps of 1 unit.

Your doctor will decide with you:

- how much Ryzodeg you will need each day and at which meal(s)
- when to check your blood sugar level and if you need a higher or lower dose.

Flexibility in dosing time

- Always follow your doctor's recommendation for dose.
- Ryzodeg can either be used once or twice each day.
- Use with the main meal(s); you can change the time of dosing as long as Ryzodeg is dosed with the largest meal(s).
- If you want to change your usual diet, check with your doctor, pharmacist or nurse first as a change in diet may alter your need for insulin.

Based on your blood sugar level, your doctor may change your dose.

When using other medicines, ask your doctor if your treatment needs to be adjusted.

Use in elderly (≥ 65 years old)

Ryzodeg can be used in elderly, but you may need to check your blood sugar level more often. Talk to your doctor about changes in your dose.

If you have kidney or liver problems

If you have kidney or liver problems, you may need to check your blood sugar level more often. Talk to your doctor about changes in your dose.

Injecting your medicine

Before you use Ryzodeg for the first time, your doctor or nurse will show you how to use the pre-filled pen.

- Check the name and strength on the label of the pen to make sure it is Ryzodeg 100 units/mL.

Do not use Ryzodeg

- in insulin infusion pumps.
- if the pen is damaged or has not been stored correctly (see section 5 'How to store Ryzodeg').
- if the insulin does not appear clear and colourless.

How to inject

- Ryzodeg is given as an injection under the skin (subcutaneous injection). Do not inject it into a vein or muscle.

- The best places to inject are the front of your waist (abdomen), upper arms or the front of your thighs.
- Change the place within the area where you inject each day to reduce the risk of developing lumps and skin pitting (see section 4).
- Always use a new needle for each injection. Re-use of needles may increase the risk of blocked needles leading to inaccurate dosing. Dispose of the needle safely after each use.
- Do not use a syringe to remove the solution from the pen to avoid dosing errors and potential overdose.

Detailed instructions for use are provided on the other side of this leaflet.

If you use more Ryzodeg than you should

If you use too much insulin, your blood sugar may get too low (hypoglycaemia), see advice in section 4 'Too low blood sugar'.

If you forget to use Ryzodeg

If you forget a dose, inject the missed dose with your next large meal on that day and thereafter resume your usual dosing schedule. Do not inject a double dose to make up for a forgotten dose.

If you stop using Ryzodeg

Do not stop using your insulin without talking to your doctor. If you stop using your insulin, this could lead to a very high blood sugar level and ketoacidosis (a condition with too much acid in the blood), see advice in section 4 'Too high blood sugar'.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Hypoglycaemia (too low blood sugar) may occur very commonly with insulin treatment (may affect more than 1 in 10 people). It can be very serious. If your blood sugar level falls too much, you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. If you have symptoms of low blood sugar, take actions to increase your blood sugar level immediately. See advice in 'Too low blood sugar' below.

If you have a serious allergic reaction (seen rarely) to the insulin or any of the ingredients in Ryzodeg, stop using this medicine and see a doctor straight away. The signs of a serious allergic reaction are:

- the local reactions spread to other parts of your body
- you suddenly feel unwell with sweating
- you start being sick (vomiting)
- you experience difficulty in breathing
- you experience rapid heartbeat or feeling dizzy.

Other side effects include:

Common (may affect up to 1 in 10 people)

Local reactions: Local reactions at the place you inject yourself may occur. The signs may include: pain, redness, hives, swelling and itching. The reactions usually disappear after a few days. See your doctor if they do not disappear after a few weeks. Stop using Ryzodeg and see a doctor straight away if the reactions become serious. For more information, see 'serious allergic reaction' above.

Uncommon (may affect up to 1 in 100 people)

Swelling around your joints: When you first start using your medicine, your body may keep more water than it should. This causes swelling around your ankles and other joints. This is usually only short-lasting.

Rare (may affect up to 1 in 1,000 people)

This medicine can cause allergic reactions such as hives, swelling of the tongue and lips, diarrhoea, nausea, tiredness and itching.

Frequency not known (cannot be estimated from the available data)

Skin changes where you use the injection (lipodystrophy): It is not known if Ryzodeg may cause lipodystrophy but such skin changes have been seen with other types of insulin. Fatty tissue under the skin may shrink (lipoatrophy) or get thicker (lipohypertrophy). Changing where you inject each time may reduce the risk of developing these skin changes. If you notice these skin changes, tell your doctor or nurse. If you keep injecting in the same place, these reactions can become more severe and affect the amount of medicine your body gets from the pen.

General effects from diabetes treatment

- Too low blood sugar (hypoglycaemia)

Too low blood sugar may happen if you:

drink alcohol; use too much insulin; exercise more than usual; eat too little or miss a meal.

Warning signs of too low blood sugar – these may come on suddenly:

Headache; slurred speech; fast heartbeat; cold sweat, cool pale skin; feeling sick, feeling very hungry; tremor or feeling nervous or worried; feeling unusually tired, weak and sleepy; feeling confused, difficulty in concentrating; short-lasting changes in your sight.

What to do if you get too low blood sugar

- Eat glucose tablets or another high sugar snack, like sweets, biscuits or fruit juice (always carry glucose tablets or a high sugar snack, just in case).
- Measure your blood sugar if possible and rest. You may need to measure your blood sugar more than once, as with all basal insulin products improvement from the period of low blood sugar may be delayed.
- Wait until the signs of too low blood sugar have gone or when your blood sugar level has settled. Then carry on with your insulin as usual.

What others need to do if you pass out

Tell everyone you spend time with that you have diabetes. Tell them what could happen if your blood sugar gets too low, including the risk of passing out.

Let them know that if you pass out, they must:

- turn you on your side
- get medical help straight away
- **not** give you any food or drink because you may choke.

You may recover more quickly from passing out with an injection of glucagon. This can only be given by someone who knows how to use it.

- If you are given glucagon, you will need sugar or a sugary snack as soon as you come round.
- If you do not respond to a glucagon injection, you will have to be treated in a hospital.
- If severe low blood sugar is not treated over time, it can cause brain damage. This can be short or long-lasting. It may even cause death.

Talk to your doctor if:

- your blood sugar got so low that you passed out
- you have used an injection of glucagon
- you have had too low blood sugar a few times recently.

This is because the dosing or timing of your insulin injections, food or exercise may need to be changed.

- Too high blood sugar (hyperglycaemia)

Too high blood sugar may happen if you:

eat more or exercise less than usual; drink alcohol; get an infection or a fever; have not used enough insulin; keep using less insulin than you need; forget to use your insulin or stop using insulin without talking to your doctor.

Warning signs of too high blood sugar – these normally appear gradually:

Flushed, dry skin; feeling sleepy or tired; dry mouth, fruity (acetone) breath; urinating more often, feeling thirsty; losing your appetite, feeling or being sick (nausea or vomiting).

These may be signs of a very serious condition called ketoacidosis. This is a build-up of acid in the blood because the body is breaking down fat instead of sugar. If not treated, this could lead to diabetic coma and eventually death.

What to do if you get too high blood sugar

- Test your blood sugar level.
- Test your urine for ketones.
- Get medical help straight away.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ryzodeg

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and carton, after 'EXP'. The expiry date refers to the last day of that month.

Before first use

Store in a refrigerator (2°C to 8°C). Do not freeze. Keep away from the freezing element. Keep the cap on the pen in order to protect from light.

After first opening or if carried as a spare

You can carry your Ryzodeg pre-filled pen (FlexTouch) with you and keep it at room temperature (not above 30°C) or in a refrigerator (2°C to 8°C) for up to 4 weeks.

Always keep the cap on the pen when you are not using it in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ryzodeg contains

- The active substances are insulin degludec and insulin aspart. Each mL of solution contains 100 units insulin degludec/insulin aspart in the ratio 70/30 (equivalent to 2.56 mg insulin degludec and 1.05 mg insulin aspart). Each pre-filled pen contains 300 units of insulin degludec/insulin aspart in 3 mL solution.
- The other ingredients are glycerol, metacresol, phenol, sodium chloride, zinc acetate, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections (see section 2).

What Ryzodeg looks like and contents of the pack

Ryzodeg is presented as a clear and colourless solution for injection in pre-filled pen (300 units per 3 mL).

Pack sizes of 1 (with or without needles), 5 (without needles) and multipack of 10 (2 x 5) (without needles) pre-filled pens of 3 mL.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Novo Nordisk A/S

Novo Allé

DK-2880 Bagsværd, Denmark

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

Instructions on how to use Ryzodeg 100 units/mL solution for injection in pre-filled pen (FlexTouch)

Please read these instructions carefully before using your FlexTouch pre-filled pen.

If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

Do not use the pen without proper training from your doctor or nurse.

Start by checking your pen to **make sure that it contains Ryzodeg 100 units/mL**, then look at the illustrations below to get to know the different parts of your pen and needle.

If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the FlexTouch pre-filled pen.

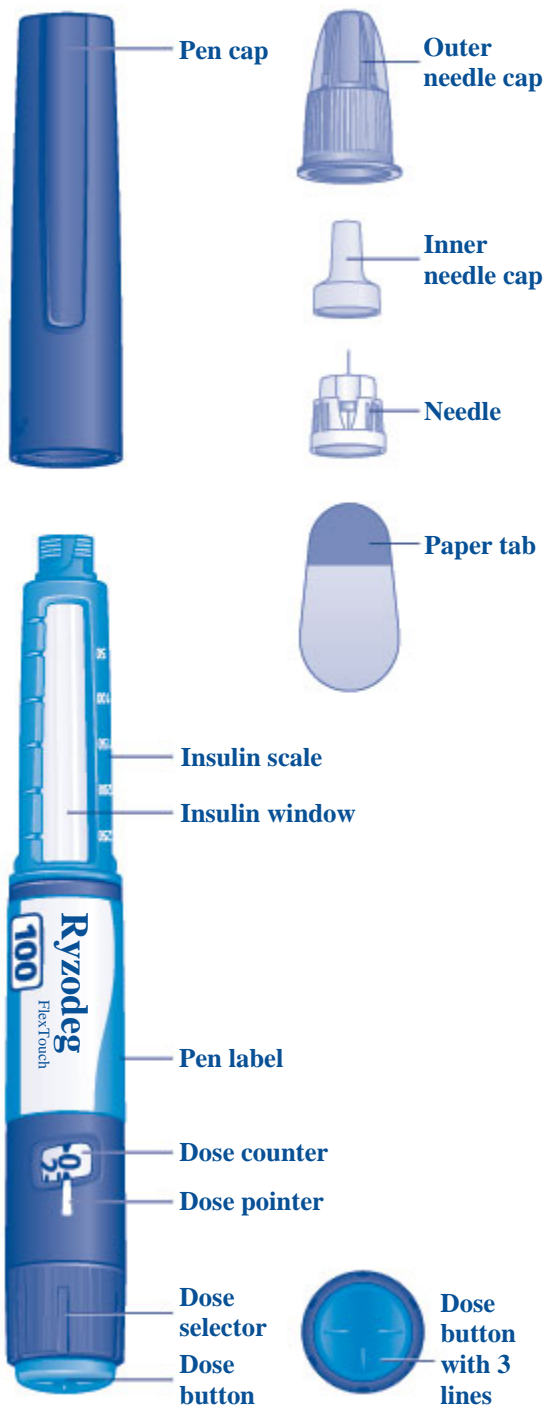
Your pen is a pre-filled dial-a-dose insulin pen containing 300 units of insulin. You can select a **maximum of 80 units per dose, in steps of 1 unit**. Your pen is designed to be used with NovoTwist or NovoFine single-use disposable needles up to a length of 8 mm.



Important information

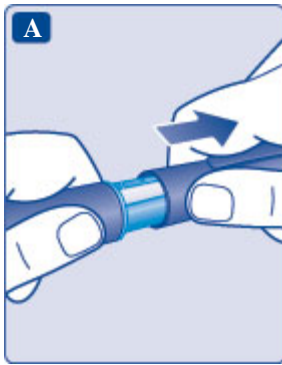
Pay special attention to these notes as they are important for correct use of the pen.

**Ryzodeg pre-filled pen and
needle (example)
(FlexTouch)**

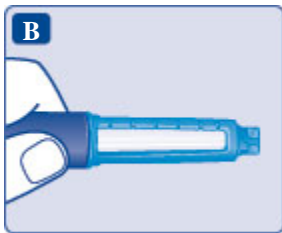


1 Prepare your pen

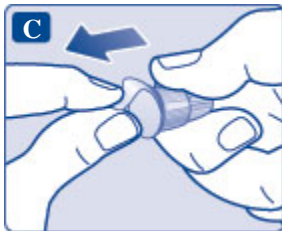
- **Check the name and strength on the label** of your pen, to make sure that it contains Ryzodeg 100 units/mL. This is especially important if you take more than one type of insulin. If you take a wrong type of insulin, your blood sugar level may get too high or too low.
- **Pull off the pen cap.**



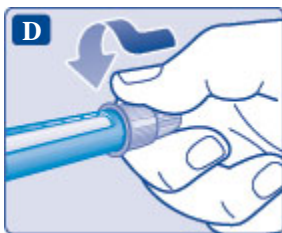
- **Check that the insulin in your pen is clear** and colourless. Look through the insulin window. If the insulin looks cloudy, do not use the pen.



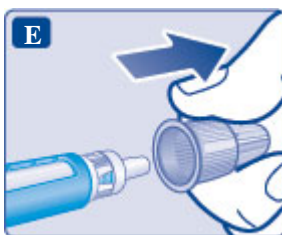
- **Take a new needle** and tear off the paper tab.



- **Push the needle straight onto the pen. Turn until it is on tight.**



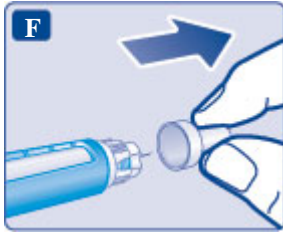
- **Pull off the outer needle cap and keep it for later.** You will need it after the injection, to correctly remove the needle from the pen.



- **Pull off the inner needle cap and throw it away.** If you try to put it back on, you may accidentally stick yourself with the needle.

A drop of insulin may appear at the needle tip. This is normal, but you must still check the insulin

flow.



⚠ Always use a new needle for each injection.
This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

⚠ Never use a bent or damaged needle.

2 Check the insulin flow

- **Always check the insulin flow before you start. This helps you to ensure that you get your full insulin dose.**
- Turn the dose selector to **select 2 units. Make sure the dose counter shows 2.**



- Hold the pen with the needle pointing up.
Tap the top of the pen gently a few times to let any air bubbles rise to the top.



- **Press and hold in the dose button** until the dose counter returns to 0.
The 0 must line up with the dose pointer.
A drop of insulin should appear at the needle tip.



A small air bubble may remain at the needle tip, but it will not be injected.

If no drop appears, repeat steps 2A to 2C up to 6 times. If there is still no drop, change the needle and repeat steps 2A to 2C once more.

If a drop of insulin still does not appear, dispose of the pen and use a new one.

⚠ Always make sure that a drop appears at the needle tip before you inject. This makes sure that the insulin flows.

If no drop appears, you will **not** inject any insulin, even though the dose counter may move. This may indicate a blocked or damaged needle.

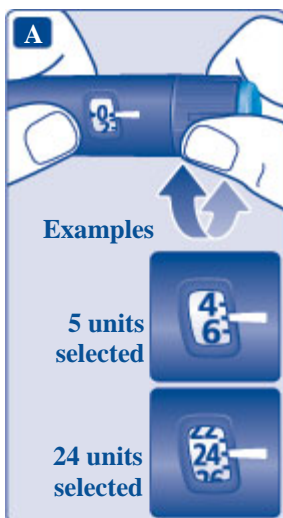
⚠ Always check the flow before you inject. If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

3 Select your dose

- **Make sure the dose counter shows 0 before you start.**
The 0 must line up with the dose pointer.
- **Turn the dose selector to select the dose you need**, as directed by your doctor or nurse.

If you select a wrong dose, you can turn the dose selector forwards or backwards to the correct dose.

The pen can dial up to a maximum of 80 units.



The dose selector changes the number of units. Only the dose counter and dose pointer will show how many units you select per dose.

You can select up to 80 units per dose. When your pen contains less than 80 units, the dose counter

stops at the number of units left.

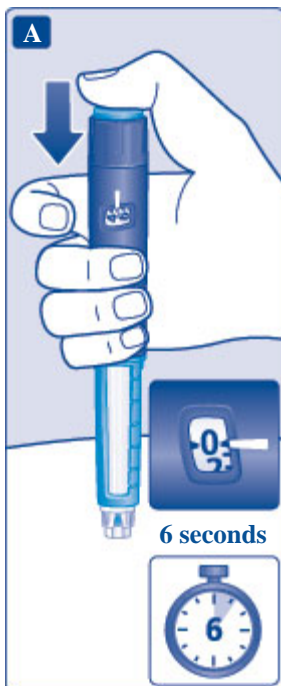
The dose selector clicks differently when turned forwards, backwards or past the number of units left. Do not count the pen clicks.

▲ Always use the dose counter and the dose pointer to see how many units you have selected before injecting the insulin.

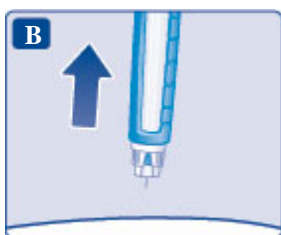
Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low. Do not use the insulin scale, it only shows approximately how much insulin is left in your pen.

4 Inject your dose

- **Insert the needle into your skin** as your doctor or nurse has shown you.
- **Make sure you can see the dose counter.**
Do not touch the dose counter with your fingers. This could interrupt the injection.
- **Press and hold down the dose button until the dose counter returns to 0.**
The 0 must line up with the dose pointer.
You may then hear or feel a click.
- **Leave the needle under the skin for at least 6 seconds** to make sure you get your full dose.



- **Pull the needle and pen straight up from your skin.**
If blood appears at the injection site, press lightly with a cotton swab. Do not rub the area.



You may see a drop of insulin at the needle tip after injecting. This is normal and does not affect your

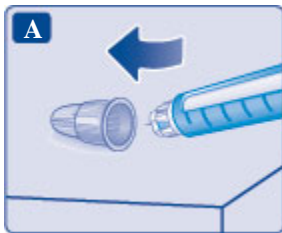
dose.

⚠ Always watch the dose counter to know how many units you inject.

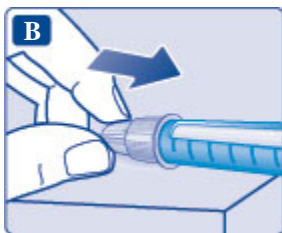
The dose counter will show the exact number of units. Do not count the pen clicks. Hold the dose button down until the dose counter returns to 0 after the injection. If the dose counter stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.

5 After your injection

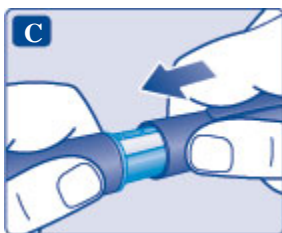
- **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer needle cap.



- Once the needle is covered, **carefully push the outer needle cap completely on.**
- **Unscrew the needle** and dispose of it carefully.



- **Put the pen cap on** your pen after each use to protect the insulin from light.



Always dispose of the needle after each injection in an appropriate sharps container. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing. If the needle is blocked, you will **not** inject any insulin.

When the pen is empty, throw it away **without** a needle on as instructed by your doctor, nurse, pharmacist or local authorities. Do not place the used needle in household waste.

⚠ Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.

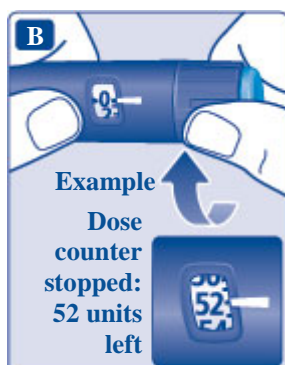
⚠ Always remove the needle after each injection and store your pen without the needle attached. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

6 How much insulin is left?

- The **insulin scale** shows you **approximately** how much insulin is left in your pen.



- **To see precisely how much insulin is left**, use the dose counter:
Turn the dose selector until the **dose counter stops**.
If it shows 80, **at least 80** units are left in your pen.
If it shows **less than 80**, the number shown is the number of units left in your pen.



- Turn the dose selector back until the dose counter shows 0.
- If you need more insulin than the units left in your pen, you can split your dose between two pens.

⚠ Be very careful to calculate correctly if splitting your dose.

If in doubt, take the full dose with a new pen. If you split the dose wrong, you will inject too little or too much insulin, which can lead to too high or too low blood sugar level.

⚠ Further important information

- **Always keep your pen with you.**
- **Always carry an extra pen and new needles** with you, in case of loss or damage.
- Always keep your pen and needles **out of sight and reach of others**, especially children.
- **Never share** your pen or your needles with other people. It might lead to cross-infection.
- **Never share** your pen with other people. Your medicine might be harmful to their health.
- Caregivers must **be very careful when handling used needles** to reduce the risk of needle injury and cross-infection.

Caring for your pen

Treat your pen with care. Rough handling or misuse may cause inaccurate dosing, which can lead to too high or too low blood sugar level.

- **Do not leave the pen in a car** or other place where it can get too hot or too cold.

- **Do not expose your pen to dust, dirt or liquid.**
- **Do not wash, soak or lubricate your pen.** If necessary, clean it with mild detergent on a moistened cloth.
- **Do not drop your pen** or knock it against hard surfaces.
If you drop it or suspect a problem, attach a new needle and check the insulin flow before you inject.
- **Do not try to refill your pen.** Once empty, it must be disposed of.
- **Do not try to repair your pen** or pull it apart.

Package leaflet: Information for the patient

Ryzodeg 100 units/mL solution for injection in cartridge 70% insulin degludec / 30% insulin aspart

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Ryzodeg is and what it is used for
2. What you need to know before you use Ryzodeg
3. How to use Ryzodeg
4. Possible side effects
5. How to store Ryzodeg
6. Contents of the pack and other information

1. What Ryzodeg is and what it is used for

Ryzodeg is used to treat diabetes mellitus in adults, adolescents and children from the age of 2 years. It helps your body reduce your blood sugar level.

This medicine contains two types of insulin:

- Basal insulin called insulin degludec, this has a long blood sugar-lowering effect.
- Rapid-acting insulin called insulin aspart, this lowers your blood sugar soon after you inject it.

2. What you need to know before you use Ryzodeg

Do not use Ryzodeg:

- if you are allergic to insulin degludec, insulin aspart or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Ryzodeg. Be especially aware of the following:

- Low blood sugar (hypoglycaemia) – if your blood sugar is too low, follow the guidance for low blood sugar in section 4.
- High blood sugar (hyperglycaemia) – if your blood sugar is too high, follow the guidance for high blood sugar in section 4.
- Switching from other insulin medicines – the insulin dose may need to be changed if you switch from another type, brand or manufacturer of insulin. Talk to your doctor.
- Pioglitazone used together with insulin, see ‘Pioglitazone’ below.
- Eye disorder – fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disorder. If you experience eye problems, talk to your doctor.
- Ensuring you use the right type of insulin – always check the insulin label before each injection to avoid accidentally confusing Ryzodeg with other insulin products.

If you have poor eyesight, please see section 3.

Children and adolescents

Ryzodeg can be used in adolescents and children from the age of 2 years with diabetes mellitus. Ryzodeg should be used with special caution in children 2 to 5 years old. The risk for very low blood sugar may be higher in this age group. There is no experience with the use of Ryzodeg in children below the age of 2 years.

Other medicines and Ryzodeg

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. Some medicines affect your blood sugar level, this may mean your insulin dose has to be changed.

Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:

- other medicines for diabetes (oral and injectable)
- sulfonamides, for infections
- anabolic steroids, such as testosterone
- beta-blockers, for high blood pressure. They may make it harder to recognise the warning signs of too low blood sugar (see section 4 'Warning signs of too low blood sugar')
- acetylsalicylic acid (and other salicylates), for pain and mild fever
- monoamine oxidase (MAO) inhibitors, for depression
- angiotensin converting enzyme (ACE) inhibitors, for some heart problems or high blood pressure.

Your blood sugar level may rise (hyperglycaemia) if you take:

- danazol, for endometriosis
- oral contraceptives (birth control pills)
- thyroid hormones, for thyroid problems
- growth hormone, for growth hormone deficiency
- glucocorticoids such as 'cortisone', for inflammation
- sympathomimetics such as epinephrine (adrenaline), salbutamol or terbutaline, for asthma
- thiazides, for high blood pressure or if your body keeps too much water (water retention).

Octreotide and lanreotide: used to treat a rare condition involving too much growth hormone (acromegaly). They may increase or decrease your blood sugar level.

Pioglitazone: oral antidiabetic medicine used to treat type 2 diabetes mellitus. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor immediately if you experience signs of heart failure such as unusual shortness of breath, rapid increase in weight or localised swelling (oedema).

If any of the above applies to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Ryzodeg with alcohol

If you drink alcohol, your need for insulin may change. Your blood sugar level may either rise or fall. You should therefore monitor your blood sugar level more often than usual.

Pregnancy and breast-feeding

It is not known if Ryzodeg affects the baby in pregnancy or during the breast-feeding. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes is needed in pregnancy.

Avoiding too low blood sugar (hypoglycaemia) is particularly important for the health of your baby.

Driving and using machines

Having too low or too high blood sugar can affect your ability to drive or use any tools or machines. If your blood sugar is too low or too high, your ability to concentrate or react might be affected. This

could be dangerous to yourself or others. Ask your doctor whether you can drive if:

- you often get too low blood sugar
- you find it hard to recognise too low blood sugar.

Important information about some of the ingredients in Ryzodeg

This medicine contains less than 1 mmol sodium (23 mg) per dose. This means that the medicine is essentially 'sodium-free'.

3. How to use Ryzodeg

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this insulin product without help. Get help from a person with good eyesight who is trained to use the pen.

Your doctor will decide with you:

- how much Ryzodeg you will need each day and at which meal(s)
- when to check your blood sugar level and if you need a higher or lower dose.

Flexibility in dosing time

- Always follow your doctor's recommendation for dose.
- Ryzodeg can either be used once or twice each day.
- Use with the main meal(s); you can change the time of dosing as long as Ryzodeg is dosed with the largest meal(s).
- If you want to change your usual diet, check with your doctor, pharmacist or nurse first as a change in diet may alter your need for insulin.

Based on your blood sugar level, your doctor may change your dose.

When using other medicines, ask your doctor if your treatment needs to be adjusted.

Use in elderly (≥ 65 years old)

Ryzodeg can be used in elderly, but you may need to check your blood sugar level more often. Talk to your doctor about changes in your dose.

If you have kidney or liver problems

If you have kidney or liver problems, you may need to check your blood sugar level more often. Talk to your doctor about changes in your dose.

Injecting your medicine

Before you use Ryzodeg for the first time, your doctor or nurse will show you how to use it.

- Please also read the manual that comes with your insulin delivery system.
- Check the name and strength on the label to make sure it is Ryzodeg 100 units/mL.

Do not use Ryzodeg

- in insulin infusion pumps.
- if the cartridge or the delivery system you are using is damaged. Take it back to your supplier. See your delivery system manual for further instructions.
- if the cartridge is damaged or has not been stored correctly (see section 5 'How to store Ryzodeg').
- if the insulin does not appear clear and colourless.

How to inject

- Ryzodeg is given as an injection under the skin (subcutaneous injection). Do not inject it into a vein or muscle.

- The best places to inject are the front of your waist (abdomen), upper arms or the front of your thighs.
- Change the place within the area where you inject each day to reduce the risk of developing lumps and skin pitting (see section 4).
- Always use a new needle for each injection. Re-use of needles may increase the risk of blocked needles leading to inaccurate dosing. Dispose of the needle safely after each use.

If you use more Ryzodeg than you should

If you use too much insulin, your blood sugar may get too low (hypoglycaemia), see advice in section 4 'Too low blood sugar'.

If you forget to use Ryzodeg

If you forget a dose, inject the missed dose with your next large meal on that day and thereafter resume your usual dosing schedule. Do not inject a double dose to make up for a forgotten dose.

If you stop using Ryzodeg

Do not stop using your insulin without talking to your doctor. If you stop using your insulin, this could lead to a very high blood sugar level and ketoacidosis (a condition with too much acid in the blood), see advice in section 4 'Too high blood sugar'.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Hypoglycaemia (too low blood sugar) may occur very commonly with insulin treatment (may affect more than 1 in 10 people). It can be very serious. If your blood sugar level falls too much, you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. If you have symptoms of low blood sugar, take actions to increase your blood sugar level immediately. See advice in 'Too low blood sugar' below.

If you have a serious allergic reaction (seen rarely) to the insulin or any of the ingredients in Ryzodeg, stop using this medicine and see a doctor straight away. The signs of a serious allergic reaction are:

- the local reactions spread to other parts of your body
- you suddenly feel unwell with sweating
- you start being sick (vomiting)
- you experience difficulty in breathing
- you experience rapid heartbeat or feeling dizzy.

Other side effects include:

Common (may affect up to 1 in 10 people)

Local reactions: Local reactions at the place you inject yourself may occur. The signs may include: pain, redness, hives, swelling and itching. The reactions usually disappear after a few days. See your doctor if they do not disappear after a few weeks. Stop using Ryzodeg and see a doctor straight away if the reactions become serious. For more information, see 'serious allergic reaction' above.

Uncommon (may affect up to 1 in 100 people)

Swelling around your joints: When you first start using your medicine, your body may keep more water than it should. This causes swelling around your ankles and other joints. This is usually only short-lasting.

Rare (may affect up to 1 in 1,000 people)

This medicine can cause allergic reactions such as hives, swelling of the tongue and lips, diarrhoea, nausea, tiredness and itching.

Frequency not known (cannot be estimated from the available data)

Skin changes where you use the injection (lipodystrophy): It is not known if Ryzodeg may cause lipodystrophy but such skin changes have been seen with other types of insulin. Fatty tissue under the skin may shrink (lipoatrophy) or get thicker (lipohypertrophy). Changing where you inject each time may reduce the risk of developing these skin changes. If you notice these skin changes, tell your doctor or nurse. If you keep injecting in the same place, these reactions can become more severe and affect the amount of medicine your body gets.

General effects from diabetes treatment

- Too low blood sugar (hypoglycaemia)

Too low blood sugar may happen if you:

drink alcohol; use too much insulin; exercise more than usual; eat too little or miss a meal.

Warning signs of too low blood sugar – these may come on suddenly:

Headache; slurred speech; fast heartbeat; cold sweat, cool pale skin; feeling sick, feeling very hungry; tremor or feeling nervous or worried; feeling unusually tired, weak and sleepy; feeling confused, difficulty in concentrating; short-lasting changes in your sight.

What to do if you get too low blood sugar

- Eat glucose tablets or another high sugar snack, like sweets, biscuits or fruit juice (always carry glucose tablets or a high sugar snack, just in case).
- Measure your blood sugar if possible and rest. You may need to measure your blood sugar more than once, as with all basal insulin products improvement from the period of low blood sugar may be delayed.
- Wait until the signs of too low blood sugar have gone or when your blood sugar level has settled. Then carry on with your insulin as usual.

What others need to do if you pass out

Tell everyone you spend time with that you have diabetes. Tell them what could happen if your blood sugar gets too low, including the risk of passing out.

Let them know that if you pass out, they must:

- turn you on your side
- get medical help straight away
- **not** give you any food or drink because you may choke.

You may recover more quickly from passing out with an injection of glucagon. This can only be given by someone who knows how to use it.

- If you are given glucagon, you will need sugar or a sugary snack as soon as you come round.
- If you do not respond to a glucagon injection, you will have to be treated in a hospital.
- If severe low blood sugar is not treated over time, it can cause brain damage. This can be short or long-lasting. It may even cause death.

Talk to your doctor if:

- your blood sugar got so low that you passed out
- you have used an injection of glucagon
- you have had too low blood sugar a few times recently.

This is because the dosing or timing of your insulin injections, food or exercise may need to be changed.

- Too high blood sugar (hyperglycaemia)

Too high blood sugar may happen if you:

eat more or exercise less than usual; drink alcohol; get an infection or a fever; have not used enough insulin; keep using less insulin than you need; forget to use your insulin or stop using insulin without talking to your doctor.

Warning signs of too high blood sugar – these normally appear gradually:

Flushed, dry skin; feeling sleepy or tired; dry mouth, fruity (acetone) breath; urinating more often, feeling thirsty; losing your appetite, feeling or being sick (nausea or vomiting).

These may be signs of a very serious condition called ketoacidosis. This is a build-up of acid in the blood because the body is breaking down fat instead of sugar. If not treated, this could lead to diabetic coma and eventually death.

What to do if you get too high blood sugar

- Test your blood sugar level.
- Test your urine for ketones.
- Get medical help straight away.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ryzodeg

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the Penfill label and carton, after 'EXP'. The expiry date refers to the last day of that month.

Before first use

Store in a refrigerator (2°C to 8°C). Do not freeze. Keep away from the freezing element.

After first opening or if carried as a spare

Do not refrigerate. You can carry your Ryzodeg cartridge (Penfill) with you and keep it at room temperature (not above 30°C) for up to 4 weeks.

Always keep Ryzodeg Penfill in the outer carton when you are not using it in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information**What Ryzodeg contains**

- The active substances are insulin degludec and insulin aspart. Each mL of solution contains 100 units insulin degludec/insulin aspart in the ratio 70/30 (equivalent to 2.56 mg insulin degludec and 1.05 mg insulin aspart). Each cartridge contains 300 units of insulin degludec/insulin aspart in 3 mL solution.
- The other ingredients are glycerol, metacresol, phenol, sodium chloride, zinc acetate, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections (see section 2).

What Ryzodeg looks like and contents of the pack

Ryzodeg is presented as a clear and colourless solution for injection in a cartridge (300 units per 3 mL).

Pack sizes of 5 and 10 cartridges of 3 mL.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Novo Nordisk A/S

Novo Allé

DK-2880 Bagsværd, Denmark

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>