NEW ZEALAND DATA SHEET

1. PRODUCT NAME

RYZODEG® 70/30 FlexTouch® solution for injection

RYZODEG® 70/30 Penfill® solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RYZODEG 70/30 is a soluble insulin product consisting of insulin degludec (ultra-long acting basal insulin) and insulin aspart (rapid acting mealtime insulin) administered in one injection.

1 mL of the solution contains 100 U insulin degludec/insulin aspart (70% soluble insulin degludec and 30% soluble insulin aspart) equivalent to 2.56 mg salt-free anhydrous insulin degludec and 1.05 mg salt-free anhydrous insulin aspart. One pre-filled pen or cartridge contains 3 mL, equivalent to 300 U of insulin degludec/insulin aspart.

Insulin degludec and insulin apart are produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

Each mL of solution contains phenol 1.5 mg and metacresol 1.72 mg as preservatives.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

RYZODEG 70/30 is a solution for injection.

RYZODEG 70/30 is a ready-to-use, clear, colourless, neutral solution in pre-filled pen or cartridge. RYZODEG 70/30 has a pH of approximately 7.4.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

For use in diabetes mellitus in patients aged 6 years and older.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

RYZODEG 70/30 is a soluble insulin product consisting of the ultra-long acting basal insulin degludec and the rapid acting prandial insulin aspart in a ratio of 70:30.

RYZODEG 70/30 can be administered once- or twice-daily with the main meal(s). However, if advised by a healthcare professional, when needed, the patient can change the time of administration as long as RYZODEG 70/30 is dosed with the main meal when taken once daily.

The potency of insulin analogues, including RYZODEG 70/30 is expressed in units (U). 1 unit (U) of RYZODEG 70/30 corresponds to 1 international unit (IU) of human insulin and one unit of most other insulin analogues.

In patients with type 2 diabetes mellitus, RYZODEG 70/30 can be administered alone, in combination with oral antidiabetic products approved for use with insulin, and in combination with bolus insulin.

In type 1 diabetes mellitus, RYZODEG 70/30 is combined with short-/rapid-acting insulin at the remaining meals.

RYZODEG 70/30 is to be dosed in accordance with individual patients' needs. Pre-meal plasma glucose levels should be used to evaluate the adequacy of the preceding dose.

Initiation

Adults with type 2 diabetes:

The recommended total daily starting dose of RYZODEG 70/30 is 10 units with meal(s) followed by individual dosage adjustments.

Patients with type 1 diabetes:

The recommended starting dose of RYZODEG 70/30 is 60-70% of the total daily insulin requirements.

RYZODEG 70/30 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

As with all insulin products, close glucose monitoring is recommended during transfer and in the following weeks. Doses and timing of concurrent rapid-acting or short-acting insulin products or other concomitant anti-diabetic treatment may need to be adjusted.

Patients with type 2 diabetes:

Patients switching from once daily basal or premix insulin therapy can be converted unit-to-unit to once daily RYZODEG 70/30 at the same total insulin dose as the patient's previous total daily insulin dose, or twice-daily RYZODEG 70/30 using half the total daily dose twice daily.

Patients switching from more than once daily basal or premix insulin therapy can be converted unit-to-unit to once daily or twice-daily RYZODEG 70/30 at the same total insulin dose as the patient's previous total daily insulin dose.

Patients switching from basal-bolus insulin therapy to RYZODEG 70/30 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:

The recommended starting dose of RYZODEG 70/30 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.

Flexibility in dosing time

RYZODEG 70/30 allows for some flexibility in the timing of insulin administration as long as it is dosed with the main meal(s).

Patients should not take an extra dose to make up for a missed dose. If a dose of RYZODEG 70/30 is missed, the patient can take the missed dose with the next main meal of that day and thereafter resume the usual dosing schedule.

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 70/30 and other insulin products.

Special populations

Elderly (≥ 65 years old)

RYZODEG 70/30 can be used in elderly patients. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis.

Renal impairment

RYZODEG 70/30 can be used in renal impaired patients. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis.

Hepatic impairment

RYZODEG 70/30 can be used in hepatic impaired patients. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis.

Paediatric population

RYZODEG 70/30 can be used in children and adolescents from the age of 6 years (see section 5.1 Clinical trials). When changing from another insulin regimen to RYZODEG 70/30, 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 Special Warnings and Precautions for Use).

RYZODEG 70/30 should be used with special caution in paediatric patients because data from the clinical trial indicate that there may be a higher risk for severe hypoglycaemia (see sections 4.4 Special Warnings and Precautions for Use, 4.8 Undesirable Effects and 5.1 Clinical trials).

Method of Administration

RYZODEG 70/30 combines the ultra-long acting basal insulin degludec and the rapid acting prandial insulin aspart in one injection.

RYZODEG 70/30 is for subcutaneous administration only. RYZODEG 70/30 must not be administered intravenously as it may result in severe hypoglycaemia. RYZODEG 70/30 must not be administered intramuscularly as it may change the absorption. RYZODEG 70/30 must not be used in insulin infusion pumps.

RYZODEG 70/30 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 and cutaneous amyloidosis (see sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects).

RYZODEG 70/30 FlexTouch® is a pre-filled pen designed to be used with NovoFine® disposable needles. FlexTouch delivers 1–80 units in increments of 1 unit.

RYZODEG 70/30 Penfill® is designed to be used with Novo Nordisk insulin delivery systems and NovoFine disposable needles.

Dosage Adjustment

As with all insulin products adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Instructions for use and handling

RYZODEG 70/30 FlexTouch: The pre-filled pen is designed to be used with NovoFine disposable needles. FlexTouch delivers 1–80 units in increments of 1 unit. The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling.

RYZODEG 70/30 Penfill: The cartridge is designed to be used with Novo Nordisk delivery systems, such as NovoPen® (durable devices for repeated use) and NovoFine disposable needles. The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling. The leaflet refers to the instructions for using the accompanying delivery system.

RYZODEG 70/30 FlexTouch and RYZODEG 70/30 Penfill is for use by one person only. The cartridge must not be refilled.

RYZODEG 70/30 must not be used if the solution does not appear clear and colourless. RYZODEG 70/30 which has been frozen must not be used.

The patient should discard the needle after each injection.

4.3. CONTRAINDICATIONS

Hypersensitivity to insulin degludec, insulin aspart or to any of the excipients.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypoglycaemia

RYZODEG 70/30 must be taken with a carbohydrate containing meal. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia.

Dose reductions and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with insulin secretagogues or GLP-1 agonists as they may potentiate the risk of hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

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.

Patients' whose blood glucose control is greatly improved, for example 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 mellitus.

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 70/30 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 may lead to diabetic ketoacidosis, which is potentially lethal.

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.

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.

Weight gain

Weight gain can occur with any insulin therapy, including RYZODEG 70/30, and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

Administration

RYZODEG 70/30 is for subcutaneous administration only. RYZODEG 70/30 must not be administered intravenously as it may result in severe hypoglycaemia. RYZODEG 70/30 must not be administered intramuscularly as it may change the absorption. RYZODEG 70/30 must not be used in insulin infusion pumps.

Skin and subcutaneous tissue disorders

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

Transfer of patients between insulin types

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.

Use in hepatic impairment

RYZODEG 70/30 can be used in hepatic impaired patients. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis.

Use in renal impairment

RYZODEG 70/30 can be used in renal impaired patients. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis.

Use in elderly

RYZODEG 70/30 can be used in elderly patients. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis.

Paediatric use

Safety and efficacy of RYZODEG 70/30 in children less than 2 years have not been established.

Avoidance of accidental mix-ups

RYZODEG 70/30 has a unique PK/PD profile and cannot be automatically substituted for any other insulin. Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between RYZODEG 70/30 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.

Effects on laboratory tests

No data available.

4.5. INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

A number of medicinal products are known to interact with glucose metabolism. Possible interactions must therefore be taken into account by the physician.

The following substances may reduce the patient's insulin requirement:

Oral antidiabetic drugs (OADs), GLP-1 receptor agonists, monoamine oxidase inhibitors (MAOIs), non-selective beta-adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids (except danazol and oxymetholone), alpha-adrenergic blocking agents, quinine, quinidine and sulphonamides.

The following substances may increase the patient's insulin requirement:

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone, diazoxide, asparaginase, nicotinic acid, oxymetholone and danazol.

Beta-blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.

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

Alcohol may intensify and prolong, or reduce the hypoglycaemic effect of insulin.

Combination of thiazolidinediones and insulin

Cases of cardiac failure have been reported when thiazolidinediones were 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 thiazolidinediones and RYZODEG 70/30 is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Thiazolidinediones should be discontinued if any deterioration in cardiac function occurs.

Incompatibilities

Substances added to RYZODEG 70/30 may cause degradation of insulin degludec and/or insulin aspart. RYZODEG 70/30 must not be added to infusion fluids. RYZODEG 70/30 must not be mixed with other medicinal products insulin products or solutions.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

In a combined fertility and embryofetal study in male and female rats, treatment with subcutaneous doses of insulin degludec up to 21 U/kg/day (yielding 5-6 times the AUC in humans at a clinical dose of 0.8 U/kg/day) prior to mating and in female rats during gestation had no effect on mating performance or fertility.

In reproductive toxicity studies, insulin aspart did not affect the fertility of male and female rats but caused a slight increase in pre-implantation loss at subcutaneous doses greater than 10 U/kg/day. Similar effects were seen with human insulin.

Use in pregnancy

Pregnancy Category: B3

There is no clinical experience with RYZODEG 70/30 in pregnant women.

In rats, decreased fetal weight was observed following treatment with insulin degludec and insulin aspart in combination at a subcutaneous dose of 30 U/kg/day (resulting in 8 and 24 times the AUC in humans for the respective insulins at a dose of 1.08 U/kg RYZODEG 70/30). In addition, an increase in fetal skeletal abnormalities was found in a rat embryofetal study conducted with insulin degludec alone. In both cases, similar effects were seen with human insulin, and are probably secondary to maternal hypoglycaemia.

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

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

Use in lactation

There is no clinical experience with RYZODEG 70/30 during breast-feeding. In rats, insulin degludec and its metabolites were secreted in milk; the peak concentration of insulin degludec in milk was less than half of that in plasma. It is unknown whether RYZODEG 70/30 is excreted in human milk. No metabolic effects of RYZODEG 70/30 are anticipated in the breast-fed newborn/infant.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

More than 2000 subjects have been exposed to RYZODEG 70/30 in the clinical development programme.

Hypoglycaemia is the most commonly observed adverse reaction in patients using insulin, including RYZODEG 70/30.

Tabulated list of adverse events and adverse reactions

Table 1: Treatment-emergent adverse events (excluding hypoglycaemia) in patients with type 1 diabetes mellitus in trial 3594 (adverse events with frequency ≥ 5%)

Adverse Event Term	RYZODEG 70/30, % (n = 362)	IDet, % (n = 180)
Nasopharyngitis	21.5	17.8
Headache	7.5	8.3
Upper respiratory tract infection	6.6	8.9
Diarrhoea	2.8	5.0

Table 2: Treatment-emergent adverse events (excluding hypoglycaemia) in patients with type 2 diabetes mellitus (adverse events with frequency ≥ 5%) with once daily treatment in trials 3590 and 3593

Adverse Event Term	RYZODEG 70/30, % (n = 495)	IGlar, % (n = 494)
Nasopharyngitis	6.9	8.3
Headache	6.9	5.7
Diarrhoea	4.6	5.1

Table 3: Treatment-emergent adverse events (excluding hypoglycaemia) in patients with type 2 diabetes mellitus (adverse events with frequency ≥ 5%) with twice-daily treatment in trials 3592 and 3597

Adverse Event Term	RYZODEG 70/30, % (n = 503)	BIAsp 30, % (n = 363)
Nasopharyngitis	15.3	11.0
Upper respiratory tract infection	7.6	8.0

Adverse Event Term	RYZODEG 70/30, % (n = 503)	BIAsp 30, % (n = 363)
Diabetic retinopathy	6.2	4.7
Headache	4.4	6.1

Adverse reactions from clinical trials

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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 4: Adverse reactions from clinical trials

System Organ Class	Preferred Term	Frequency
Immune system disorders	Hypersensitivity	Rare
	Urticaria	Rare
Metabolism and nutrition disorders	Hypoglycaemia	Very common
Skin and subcutaneous tissue disorders	Lipodystrophy	Not known
General disorders and administration site conditions	Injection site reactions	Common
	Peripheral oedema	Uncommon

Adverse reactions from post-marketing sources

Adverse reactions listed below are based on post-marketing source data and classified according to MedDRA System Organ Class.

Table 5: Adverse reactions from post-marketing sources

System Organ Class	Preferred Term	Frequency
Skin and subcutaneous tissue disorders	Cutaneous amyloidosis	Not known

Description of selected adverse reactions

Immune system disorders

As with any insulin therapy, allergic reactions may occur. Immediate type allergic reactions to either insulin itself or the excipients may potentially be life threatening. With RYZODEG 70/30 hypersensitivity (manifested with swelling of tongue and lips, diarrhoea, nausea, tiredness and itching) and urticaria were reported rarely.

Hypoglycaemia

As with any insulin therapy, 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.

Injection site reactions

As may occur with any insulin therapy, injection site reactions (including injection site haematoma, pain, haemorrhage, erythema, nodules, swelling, discolouration, pruritus, warmth and injection site mass) occurred in subjects treated with RYZODEG 70/30. These reactions are usually mild and transitory and they normally disappear during continued treatment.

Skin and subcutaneous tissue disorders

As with any insulin therapy, lipodystrophy (including lipohypertrophy and lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4 Special Warnings and Precautions for Use).

Peripheral oedema

Insulin, including RYZODEG 70/30, may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Antibody production

There was no clinically relevant development of insulin antibodies after long-term treatment with RYZODEG 70/30.

Paediatric population

RYZODEG 70/30 has been administered to children (6-11 years) and adolescents (12-18 years) for the investigation of pharmacokinetic properties (see section 5.2 Pharmacokinetic Properties). Clinical trials have been performed in children aged 2 to 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 (see sections 4.2 Dose and Method of Administration, 4.4 Special Warnings and Precautions for Use' and 'Clinical trials').

Other special populations

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at https://nzphvc.otago.ac.nz/reporting.

4.9. OVERDOSE

A specific overdose for insulin cannot be defined; however, hypoglycaemia may develop over sequential stages if doses are administered which are too high relative to the patient's requirements:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose. It is therefore recommended that the patient always carries glucose-containing products. Adjustments in drug dosage, meal patterns, or exercise may be needed.
- Severe hypoglycaemic episodes, including where the patient is not able to treat themselves, 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. After apparent clinical recovery from hypoglycaemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycaemia.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

ATC code: A10AD06

Mechanism of action

Insulin degludec and insulin aspart bind to the human insulin receptor, resulting 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.

The pharmacodynamic effect of RYZODEG 70/30 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 ultra-long acting insulin degludec. The ultra-long acting basal component of RYZODEG 70/30 (insulin degludec) forms soluble multi-hexamers upon subcutaneous injection of RYZODEG 70/30 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 70/30 has a rapid onset of action occurring soon after injection providing mealtime coverage while the basal component has a flat, stable and ultra-long action profile providing continuous coverage of the basal insulin requirements. The duration of action of a single dose of RYZODEG 70/30 is beyond 24 hours.

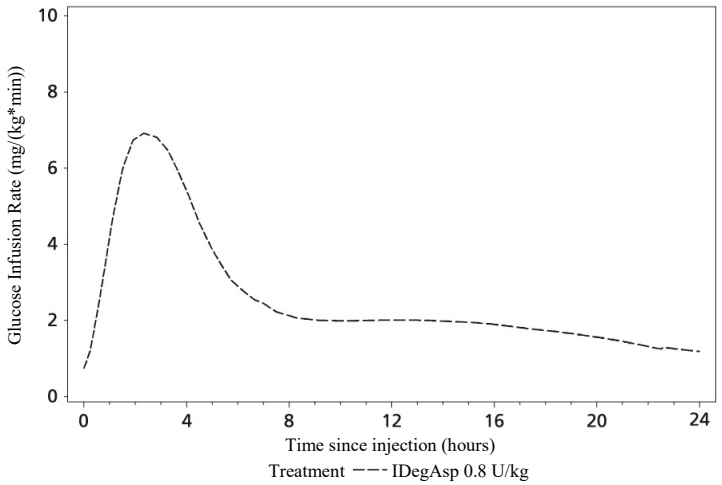


Figure 1: Mean glucose infusion rate (GIR) profile of RYZODEG 70/30 after single dose administration of 0.8 U/kg in type 1 diabetes mellitus (trial 3539)

The total and maximum glucose-lowering effects of RYZODEG 70/30 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 RYZODEG 70/30 between elderly and younger subjects.

Clinical trials

Five (plus one extension) multi-national, randomised, controlled, open-label, treat-to-target clinical trials of 26 weeks or 52 weeks duration were conducted exposing a total of 1360 subjects with diabetes mellitus (362 subjects in type 1 diabetes mellitus and 998 subjects in type 2 diabetes mellitus) to RYZODEG 70/30. RYZODEG 70/30 administered once daily plus oral antidiabetic drugs (OADs) was compared to insulin glargine (IGlar) once daily plus OADs in two trials in type 2 diabetes mellitus. RYZODEG 70/30 once daily plus insulin aspart (IAsp) was also compared to once daily or twice-daily insulin detemir (IDet) plus IAsp in type 1 diabetes mellitus. RYZODEG 70/30 twice daily plus OADs was compared to biphasic insulin aspart 30 (BIAsp 30) twice daily plus OADs in two trials in type 2 diabetes mellitus. BIAsp 30 is a white suspension for subcutaneous injection consisting of 30% soluble insulin aspart and 70% protamine-crystallised insulin aspart, marketed as NovoMix® 30.

Efficacy and safety of once daily and twice daily mealtime dosing of RYZODEG 70/30 either for insulin initiation or insulin intensification were confirmed. RYZODEG 70/30 effectively improved glycaemic control as measured by HbA_{1c}. Non-inferiority of change from baseline to end-of-trial of HbA_{1c} was confirmed in all trials against all comparators, when treating subjects to target. All trials comparing insulin products were carried out using a treat-to-target design, where titration of basal insulin was based on pre-breakfast glucose values in order to achieve similar degrees of glycaemic control allowing for objective comparison of overall safety profile of the tested insulins, including risk of hypoglycaemia.

In a non-blinded, treat-to-target clinical trial (trial 3590), insulin-naïve adult subjects with type 2 diabetes mellitus were randomised to 26 weeks of treatment with RYZODEG 70/30 + metformin (Met) or IGlar + Met. RYZODEG 70/30 was administered once daily at breakfast. IGlar was administered once daily according to approved labelling. All subjects started on 10U

of either RYZODEG 70/30 or IGlar. RYZODEG 70/30 and IGlar groups had similar HbA_{1c} levels with IGlar resulting in lower fasting plasma glucose (FPG) levels. Treatment with RYZODEG 70/30 resulted in higher rates of confirmed hypoglycaemia but lower rates of nocturnal confirmed hypoglycaemia compared to IGlar (see Table 6).

In a non-blinded, treat-to-target clinical trial (trial 3593), adult subjects with type 2 diabetes mellitus who were inadequately controlled with basal insulin once daily + OADs were randomised to 26 weeks of treatment with RYZODEG 70/30 once daily or IGlar once daily, both in combination with Met ± pioglitazone (Pio) ± DPP-4 inhibitor. All subjects initiated trial insulin treatment by switching on a unit-to-unit basis from the basal insulin they received before randomisation. Subjects administered RYZODEG 70/30 once daily with either the evening meal or the largest meal or administered IGlar once daily according to approved labelling. RYZODEG 70/30 and IGlar groups had similar HbA_{1c} and FPG levels. Treatment with RYZODEG 70/30 resulted in higher rates of confirmed hypoglycaemia but similar rates of nocturnal confirmed hypoglycaemia compared to IGlar (see Table 6).

The use of RYZODEG 70/30 in combination with sulphonylureas, GLP-1 agonists, alpha-glucosidase inhibitors and SGLT-2 inhibitors has not been studied.

Table 6: Results of two 26-weeks trials of RYZODEG 70/30 once daily versus insulin glargine once daily in type 2 diabetes mellitus

	Trial 3590		**Trial 3593**	
	RYZODEG 70/30 once daily + Metformin Insulin naïve	IGlar once daily + Metformin Insulin naïve	RYZODEG 70/30 once daily + Metformin ± pioglitazone ± DPP-4 inhibitor Insulin users	IGlar once daily + Metformin ± pioglitazone ± DPP-4 Insulin users
n	266	263	230	233
Mean HbA_{1c} (%)				
End of trial Mean change from baseline	7.2 -1.65	7.2 -1.72	7.3 -0.98	7.4 -1.00
Estimated treatment difference [95% CI] RYZODEG 70/30 once daily minus IGlar once daily	0.03 [-0.14;0.20]		-0.03 [-0.20;0.14]	
Fasting Plasma Glucose (FPG) in mmol/L				
End of trial Mean change from baseline	6.8 -3.32	6.3 -4.02	6.3 -1.68	6.0 -1.88
Estimated treatment difference [95% CI] RYZODEG 70/30 once daily minus IGlar once daily	0.51 [0.09;0.93]		0.33 [-0.11;0.77]	
End-of-Trial Prandial Blood Glucose Increment (Plasma) in mmol/L				
90 minutes Post Breakfast Mean change from baseline	1.9 -1.5	3.4 -0.3		
90 minutes Post Dinner Mean change from baseline			1.2 -1.5	2.6 -0.6
Hypoglycaemia Rate per Patient year of exposure				
Severe hypoglycaemia	0.01	0.01	0.00	0.04

Confirmed hypoglycaemia	4.23	1.85	4.31	3.20
Treatment ratio [95%] RYZODEG 70/30 once daily/IGlar once daily	2.17 [1.59;2.94]		1.43 [1.07;1.92]	
Nocturnal confirmed hypoglycaemia	0.19	0.46	0.82	1.01
Treatment ratio [95%] RYZODEG 70/30 once daily/IGlar once daily	0.29 [0.13;0.65]		0.80 [0.49;1.30]	

(n = no. of subjects in the full analysis set (FAS))

In a non-blinded, treat-to-target clinical trial (trial 3592), adult subjects with type 2 diabetes mellitus who were inadequately controlled on once daily or twice daily premixed or self-mixed insulin regimen ± OADs were randomised to 26 weeks of treatment with RYZODEG 70/30 twice daily or BIAsp 30 twice daily, both ± Met, ± DPP-4 inhibitor, ± Pio. RYZODEG 70/30 and BIAsp 30 were administered before the breakfast and main evening meals. Subjects on premixed insulin twice daily transferred their doses unit-to-unit to trial insulin. Subjects on a self-mixed regimen transferred to trial insulin at doses corresponding to their respective self-mixed pre-meal dose. Subjects previously receiving premixed or self-mixed insulin once daily were to divide their dose into 2 equal doses. RYZODEG 70/30 and BIAsp 30 groups had similar HbA_{1c} levels with RYZODEG 70/30 resulting in significantly lower FPG levels. Treatment with RYZODEG 70/30 resulted in significantly lower rates of confirmed hypoglycaemia and lower rates of nocturnal confirmed hypoglycaemia compared to BIAsp 30 (see Table 7).

In a non-blinded, treat-to-target clinical trial (trial 3597), Asian adult subjects with type 2 diabetes mellitus who were inadequately controlled on basal insulin, premixed or self-mixed insulin in an once daily or twice daily insulin regimen ± Met were randomised to 26 weeks of treatment with RYZODEG 70/30 twice daily or BIAsp 30 twice daily, with or without Met. Subjects on once daily insulin split the total dose of their previous insulin treatment into 2 equal doses of trial insulin for twice daily administration. Subjects on twice daily insulin transferred their doses on a unit-to-unit basis to the trial insulin. RYZODEG 70/30 and BIAsp 30 was administered at the breakfast and main evening meal. RYZODEG 70/30 and BIAsp 30 groups had similar HbA_{1c} levels with RYZODEG 70/30 resulting in significantly lower FPG levels. Treatment with RYZODEG 70/30 resulted in similar rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia compared to BIAsp 30 (see Table 7).

Table 7: Results of two 26-weeks trials of RYZODEG 70/30 versus BIAsp 30 in type 2 diabetes mellitus

	Trial 3592		**Trial 3597**	
	RYZODEG 70/30 twice daily ± metformin ± pioglitazone ± DPP-4 inhibitor Insulin users	BIAsp 30 twice daily ± metformin ± pioglitazone ± DPP-4 inhibitor Insulin users	RYZODEG 70/30 twice daily ± metformin Insulin users	BIAsp 30 twice daily ± metformin Insulin users
n	224	222	280	142
Mean HbA_{1c} (%)				
End of trial Mean change from baseline	7.1 -1.28	7.1 -1.30	7.1 -1.38	7.0 -1.42

Estimated treatment difference [95% CI] RYZODEG 70/30 twice daily minus BIAsp 30 twice daily	-0.03 [-0.18;0.13]		0.05 [-0.10;0.20]	
FPG in mmol/L				
End of trial Mean change from baseline	5.8 -3.09	6.8 -1.76	5.4 -2.55	6.5 -1.47
Estimated treatment difference [95% CI] RYZODEG 70/30 twice daily minus BIAsp 30 twice daily	-1.14 [-1.53;-0.76]		-1.06 [-1.43;-0.70]	
Hypoglycaemia Rate per Patient year of exposure				
Severe hypoglycaemia	0.09	0.25	0.05	0.03
Confirmed hypoglycaemia	9.72	13.96	9.56	9.52
Treatment ratio [95%] RYZODEG 70/30 twice daily/BIAsp 30 twice daily	0.68 [0.52;0.89]		1.00 [0.76;1.32]	
Nocturnal confirmed hypoglycaemia	0.74	2.53	1.11	1.55
Treatment ratio [95%] RYZODEG 70/30 twice daily/BIAsp 30 twice daily	0.27 [0.18;0.41]		0.67 [0.43;1.06]	

(n = no. of subjects in the FAS)

In a non-blinded, treat-to-target clinical trial (trial 3594), adult subjects with type 1 diabetes mellitus were randomised to 26 weeks of treatment with RYZODEG 70/30 and IAsp or IDet and IAsp. RYZODEG 70/30 was administered once daily with any main meal while allowing for a switch to another main meal. IAsp was administered for the remaining insulin requiring meals. IDet was administered once daily at evening meal or bedtime. A second dose of IDet was added to breakfast after 8 weeks in cases of inadequate glycaemic control (mean pre-dinner PG > 6.0 mmol/L, deterioration of HbA_{1c} from baselines < 8.0% or improvement of HbA_{1c} <0.5% when baseline HbA_{1c} ranges from 8.0-10%). RYZODEG 70/30 and IDet groups had similar HbA_{1c} and FPG levels and similar rates of confirmed hypoglycaemia. Treatment with RYZODEG 70/30 resulted in lower rates of nocturnal confirmed hypoglycaemia compared to IDet (see Table 8).

Table 8: Results of a 26 week trial with RYZODEG 70/30 versus insulin detemir in type 1 diabetes mellitus

	Trial 3594	
	RYZODEG 70/30 once daily + IAsp	IDet once daily/twice daily + IAsp
n	366	182
Mean HbA_{1c} (%)		
End of trial Mean change from baseline	7.6 -0.73	7.6 -0.68
Estimated treatment difference [95% CI] RYZODEG 70/30 once daily minus IDet once daily/twice daily	-0.05 [-0.18;0.08]	
FPG in mmol/L		
End of trial Mean change from baseline	8.7 -1.61	8.6 -2.41
Estimated treatment difference [95% CI] RYZODEG 70/30 once daily minus IDet once daily/twice daily	0.23 [-0.46;0.91]	
Hypoglycaemia Rate per Patient year of exposure		

Severe hypoglycaemia	0.33	0.42
Confirmed hypoglycaemia	39.2	44.3
Treatment ratio [95%] RYZODEG 70/30 once daily/ IDet once daily/twice daily	0.91 [0.76;1.09]	
Nocturnal confirmed hypoglycaemia	3.71	5.72
Treatment ratio [95%] RYZODEG 70/30 once daily/ IDet once daily/twice daily	0.63 [0.49;0.81]	

(n = no. of subjects in the FAS)

Paediatric population

The efficacy and safety of RYZODEG 70/30 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 70/30 arm included 40 exposed children aged 2-5 years, 61 children aged 6-11 years and 80 adolescents aged 12-17 years. RYZODEG 70/30 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 70/30 and insulin detemir arms, respectively.

Table 9: Mean change in HbA1c at week 16 for RYZODEG 70/30 versus insulin detemir in paediatric patients with type 1 diabetes mellitus

	Trial 3816			
	RYZODEG 70/30 once daily + IAsp		IDet once daily/twice daily + IAsp	
	N	Mean (SD)	N	Mean (SD)
1 – 5 years	40	-0.4 (1.0)	41	-0.5 (0.8)
6 – 11 years	61	-0.1 (1.0)	61	-0.3 (0.9)
12 – 17 years	80	-0.3 (1.0)	77	-0.1 (1.0)

Table 10: Hypoglycaemia rates in a 16 week trial with RYZODEG 70/30 versus insulin detemir in paediatric patients with type 1 diabetes mellitus

	Trial 3816									
	RYZODEG 70/30 once daily + IAsp					IDet once daily/twice daily + IAsp				
	N	n	%	E	R	N	n	%	E	R
Confirmed Hypoglycaemia										
1 – 5 years	40	39	97.5	520	4335	41	37	90.2	559	4564
6 – 11 years	61	56	91.8	960	5140	61	58	95.1	1065	5809
12 – 17 years	80	73	91.3	1052	4366	77	69	89.6	1048	4490
Severe Hypoglycaemia										
1 – 5 years	40	4	10.0	5	42	41	2	4.9	2	16
6 – 11 years	61	3	4.9	4	21	61	0	0.0	0	0
12 – 17 years	80	4	5.0	5	21	77	1	1.3	2	9
Nocturnal Confirmed Hypoglycaemia										

1 – 5 years	40	18	45.0	55	459	41	21	51.2	52	425
6 – 11 years	61	38	62.3	108	578	61	34	55.7	85	464
12 – 17 years	80	45	56.3	153	635	77	51	66.2	154	660

N = Number of patients

n = number of patients experiencing an event

%: Percentage of Subjects with the Event

E: Number of Events

R: Event Rate per 100 Patient Year(s) of Exposure

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 70/30 in adolescent patients with type 2 diabetes mellitus.

Cardiovascular evaluation

DEVOTE was a randomised, double-blind, active-controlled, treat-to-target and event-driven clinical trial with a median duration of 2 years comparing the cardiovascular safety of insulin degludec versus insulin glargine (100 units/ml) in 7,637 patients with type 2 diabetes mellitus at high risk of cardiovascular events. Patients eligible to enter the trial were 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure (85% of the enrolled population) or were 60 years of age or older and had other specified risk factors for cardiovascular disease (15% of the enrolled population).

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 of MACE comparing insulin degludec to insulin glargine. The cardiovascular safety of insulin degludec as compared to insulin glargine was confirmed (Figure 2).

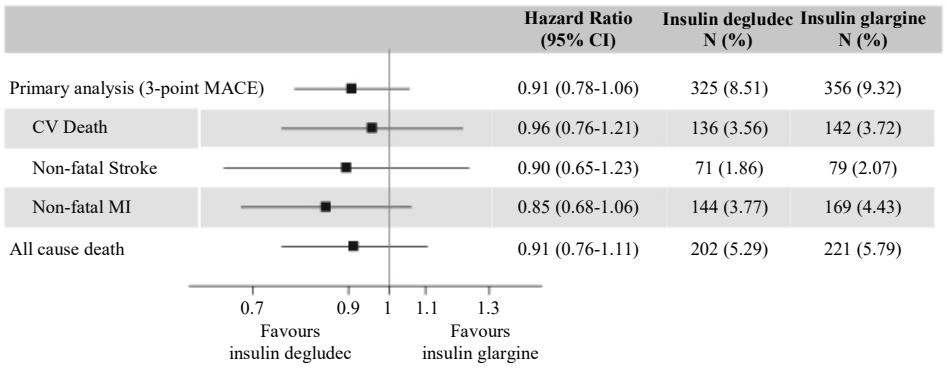


Figure 2: Forest plot of analysis of the composite 3-point MACE and individual cardiovascular endpoints in DEVOTE

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

The cardiovascular safety of insulin degludec as compared to insulin glargine (100 units/ml) was confirmed (HR: 0.91; 95% CI [0.78;1.06], p = 0.209).

Similar improvements in HbA_{1c} were achieved with insulin degludec and insulin glargine, and a greater reduction in FPG was achieved with insulin degludec.

Insulin degludec was superior compared to insulin glargine in terms of a lower rate of severe hypoglycaemic events and a lower proportion of subjects experiencing severe hypoglycaemia. The rate of nocturnal severe hypoglycaemia was significantly lower for insulin degludec compared to insulin glargine.

Physicochemical Properties

Insulin degludec

Insulin degludec differs from human insulin in that the threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached (chemical name: LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin).

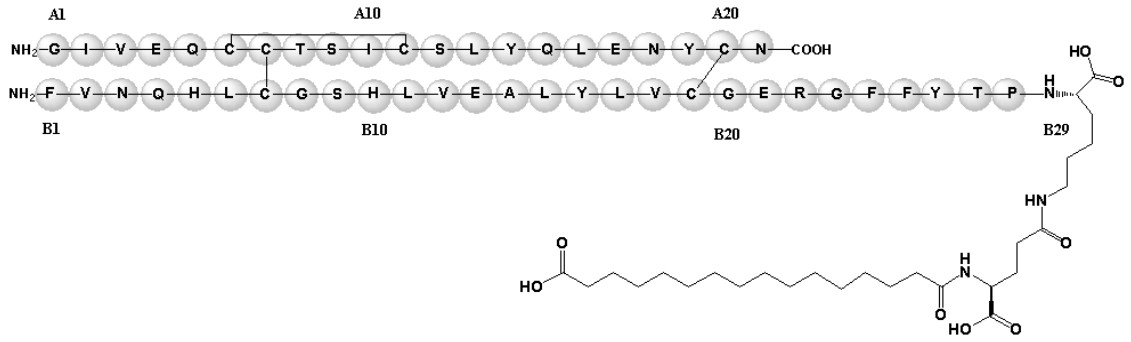
Insulin aspart

Insulin aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28.

Chemical structure

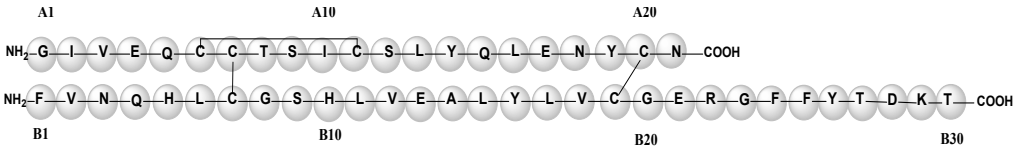
Insulin degludec

Insulin degludec has a molecular formula of $C_{274}H_{411}N_{65}O_{81}S_6$ and a molecular weight of 6103.97 daltons.



Insulin aspart

Insulin aspart has a molecular formula of $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8 daltons.



CAS number

Insulin degludec: 844439-96-9.

Insulin aspart: 116094-23-6.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

After subcutaneous injection, soluble and stable multi-hexamers of insulin degludec are formed creating a depot 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 resulting in a slow and continuous delivery of insulin degludec into the circulation. Steady-state serum concentrations of the ultra-long acting component (insulin degludec) is reached after 2-3 days of daily RYZODEG 70/30 administration. The rapid absorption characteristics of the well established insulin aspart are maintained by RYZODEG 70/30. 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.

Metabolism

Degradation of insulin degludec and insulin aspart is similar to that of human insulin.

Excretion

The half-life after subcutaneous administration of RYZODEG 70/30 is determined by the rate of absorption from the subcutaneous tissue. The half-life of the basal component, insulin degludec, at steady-state is approximately 25 hours independent of dose.

Linearity

Total exposure with RYZODEG 70/30 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.

Special populations

Elderly, race, renal and hepatic impairment

There are no clinically relevant differences in the pharmacokinetics of RYZODEG 70/30 between elderly and younger adult subjects, between races or between healthy subjects and subjects with renal or hepatic impairment.

Gender

There are no gender differences in the pharmacokinetic properties of RYZODEG 70/30.

Paediatric population

The pharmacokinetic properties of RYZODEG 70/30 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 pharmacokinetics properties of the insulin degludec component of RYZODEG 70/30 were investigated using 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.

At steady state, the pharmacokinetic properties of insulin degludec in children (1-11 years) and adolescents (12-18 years) were 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

Genotoxicity

Genotoxicity studies have not been carried out with insulin degludec. Insulin aspart did not cause gene mutations, chromosomal damage or DNA damage in a range of genotoxicity tests.

Carcinogenicity

Standard 2-year carcinogenicity studies in animals have not been performed with insulin degludec and insulin aspart, either alone or in combination.

In a 52-week study with insulin degludec, rats received subcutaneous doses of up to 10 U/kg/day (resulting in 5 times the AUC in humans at a dose of 0.8 U/kg/day). No treatment-related increases in incidences of hyperplasia, benign or malignant tumours were recorded, and no treatment-related changes in female mammary gland cell proliferation were found using BrdU incorporation. *In vitro* studies showed the ratio of mitogenic relative to metabolic potency for insulin degludec is unchanged compared to human insulin.

In 52-week repeat dose toxicity studies with insulin aspart in Sprague-Dawley rats at subcutaneous doses up to 50 U/kg/day, the only significant toxicity findings were related to hypoglycaemia. At a higher dose of 200 U/kg/day in female Sprague-Dawley rats, insulin aspart, like human insulin, caused induction of mammary tumours. The clinical relevance of these findings is not known. Neither clinical nor epidemiological studies conducted to date have shown an association between insulin use and carcinogenesis but the available evidence is considered too limited to be conclusive at this time. *In vitro* studies showed that the mitogenic activity of insulin aspart does not differ from that observed with human insulin.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

RYZODEG 70/30 contains the following inactive ingredients: glycerol, sodium chloride, zinc acetate, hydrochloric acid and sodium hydroxide for pH adjustment, metacresol and phenol as preservatives, and water for injections.

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

Unopened: 30 months.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Before use:

FlexTouch and Penfill

Store at 2°C to 8°C. Refrigerate. Do not freeze. Store RYZODEG 70/30 away from the freezing element in the refrigerator.

In-use or carried as a spare:

FlexTouch

Store below 30°C or in the refrigerator between 2°C to 8°C for up to 28 days. Keep the cap on the pen in order to protect from light. Protect from heat.

Penfill

Store below 30°C for up to 28 days. Do not refrigerate. Keep cartridges in the outer carton in order to protect from light. Protect from heat.

6.5. Nature and Contents of Container

RYZODEG 70/30 FlexTouch: 3 mL solution in cartridge (type 1 glass) with a plunger (halobutyl) and a stopper (halobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene.

Pack sizes: 5 x 3 mL.

RYZODEG 70/30 Penfill: 3 mL solution in cartridge (type 1 glass) with a plunger (halobutyl) and a stopper (halobutyl/polyisoprene) in a carton.

Pack size: 5 x 3 mL.

Not all pack sizes may be marketed.

6.6. Special Precautions for Disposal

The patient should be advised to discard the injection needle after each injection in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Novo Nordisk Pharmaceuticals Ltd
PO Box 51-268
Pakuranga
Auckland
Tel: 0800 733 737
Fax: +6499165595

9. DATE OF FIRST APPROVAL

1 June 2023

10. DATE OF REVISION OF THE TEXT

Summary table of changes

Section changed	Summary of new information