ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Kyinsu (700 units + 2 mg)/mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution contains 700 units of insulin icodec* and 2 mg of semaglutide*.

Each pre-filled pen contains 300 units of insulin icodec and 0.86 mg of semaglutide in 0.43 mL solution.
Each pre-filled pen contains 700 units of insulin icodec and 2 mg of semaglutide in 1 mL solution.
Each pre-filled pen contains 1 050 units of insulin icodec and 3 mg of semaglutide in 1.5 mL solution.

10 dose steps contain 10 units of insulin icodec and 0.029 mg of semaglutide.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (FlexTouch).

Clear, colourless or almost colourless, isotonic solution with a pH of approximately 7.4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kyinsu is indicated for the treatment of adults with type 2 diabetes mellitus insufficiently controlled on basal insulin or glucagon-like peptide 1 (GLP-1) receptor agonists as an adjunct to diet and exercise in addition to oral antidiabetic medicinal products.
For study results with respect to combinations, effects on glycaemic control, and the populations studied, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology

Kyinsu is given once weekly by subcutaneous administration.
Kyinsu is intended to be administered on the same day of the week. Kyinsu can be administered at any time of the day.

Kyinsu is administered as dose steps.
Ten (10) dose steps contain 10 units of insulin icodec and 0.029 mg of semaglutide.
The dose counter on the pen shows the number of dose steps.

The maximum recommended weekly dose is 350 dose steps, i.e. 350 units insulin icodec and 1 mg semaglutide.

Kyinsu should be dosed according to individual patient´s needs. It is recommended to optimise glycaemic control by adjusting the dose based on self-monitored fasting plasma glucose.

Due to the long half-life of Kyinsu, adjustment of dose is not advised during acute illness nor if patients make short-term changes in their physical activity level or usual diet. In these situations, patients should be instructed to consult their health care professional for further guidance on other applicable adjustments, e.g. glucose intake or changes to other glucose lowering medicinal product(s).

Initiation of Kyinsu

Treatment with basal insulin or GLP-1 receptor agonist should be discontinued prior to initiation of Kyinsu. The recommended starting dose of Kyinsu is 40 dose steps (40 units of insulin icodec and 0.114 mg of semaglutide), followed by individual once-weekly dose adjustments. Frequent glucose monitoring is recommended during the switch and in the subsequent weeks.

When Kyinsu is added to sulfonylurea treatment, discontinuation or a reduction in the dose of sulfonylurea should be considered.

Switch from a daily basal insulin, or a daily GLP-1 receptor agonist
When switching from a daily basal insulin, or a daily GLP-1 receptor agonist, treatment with Kyinsu should be initiated on the day following the last administered dose of the previous daily regimen (see section 4.4).

When switching from a daily basal insulin to Kyinsu, adjustments of other antidiabetic medicinal products may be considered. Blood glucose should be closely monitored (see section 4.4).

Switch from once weekly basal insulin
There is no experience from switching from a weekly basal insulin to Kyinsu. When switching from a weekly basal insulin, the time of treatment initiation with Kyinsu should be based on the individual patient’s fasting plasma glucose one week after the last administered dose of weekly basal insulin.

Switch from once weekly GLP-1 receptor agonist
When switching from a weekly GLP-1 receptor agonist, treatment with Kyinsu should be initiated one week after the last administered dose of the previous weekly GLP-1 receptor agonist treatment.

Dose titration

Kyinsu should be dosed according to individual patient’s needs.
It is recommended to optimise glycaemic control via dose adjustment once weekly based on fasting plasma glucose (see section 5.1).

Adjustment of the dose should be made based on the self-monitored fasting plasma glucose on the day of titration and the two prior days.

Missed dose

If a dose is missed, it should be administered as soon as possible. If it is still within 3 days of the missed dose, the patient can then resume their original once weekly dosing schedule.

If more than 3 days have passed, the missed dose should still be administered as soon as possible. The once weekly dosing schedule will then be changed to the day of the week where the missed dose was administered. If the original day of once-weekly administration is to be maintained, the time between subsequent doses can be successively extended to finally obtain the same administration day.

Special populations

Elderly
No dose adjustment is required for elderly patients (see section 5.2).

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2). In patients with renal impairment, more frequent glucose monitoring is recommended.
Kyinsu is not recommended for use in patients with end-stage renal disease, due to limited data with the semaglutide mono-component (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with hepatic impairment (see section 5.2). In patients with hepatic impairment, more frequent glucose monitoring is recommended.
Experience with the use of Kyinsu in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with Kyinsu.

Paediatric population
The safety and efficacy of Kyinsu in children and adolescents below 18 years have not been established. No data are available.

Method of administration

Subcutaneous use only.

Kyinsu must not be administered intravenously as it may result in severe hypoglycaemia.
Kyinsu must not be administered intramuscularly as it may change the absorption.
Kyinsu must not be used in insulin infusion pumps.
Kyinsu must not be drawn from the cartridge of the pre-filled pen into a syringe (see section 4.4).

Kyinsu is administered subcutaneously by injection in the thigh, the upper arm, or the abdominal wall. Injection sites should always be rotated within the same region to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4).

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

Kyinsu is available in a pre-filled pen.
The dose counter shows the number of dose steps of Kyinsu to be injected.
No dose recalculation is required.

The pre-filled pens of Kyinsu can provide the following doses:
- The pre-filled pen of 0.43 mL delivers 10–300 dose steps in one injection in increments of 10 dose steps.
- The pre-filled pen of 1 mL delivers from 10–350 dose steps in one injection in increments of 10 dose steps.
- The pre-filled pen of 1.5 mL delivers from 10–350 dose steps in one injection in increments of 10 dose steps.

For further information before administration, see section 6.6.

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General

Kyinsu should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV.

Hypoglycaemia

Hypoglycaemia may occur if the dose of Kyinsu is higher than required (see sections 4.5, 4.8 and 4.9). Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.

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.

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

Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring. These include change in physical activity, change in diet or missed meals, alcohol consumption, concomitant treatment with certain other medicinal products (see section 4.5), illness, improved insulin sensitivity (e.g. by removal of stress factors or weight change), change in the injection area, and certain uncompensated endocrine disorders.

The prolonged effect of basal insulins may delay recovery from hypoglycaemia. Upon onset of a hypoglycaemic episode, patient is recommended to closely measure blood glucose until recovery.

Gastrointestinal adverse reactions

Use of GLP-1 receptor agonists like semaglutide, a mono-component of Kyinsu, may be associated with gastrointestinal adverse reactions (see section 4.8). This should be considered when treating patients with impaired renal function, as nausea, vomiting, and diarrhoea may cause dehydration which could cause a deterioration of renal function. Patients should be advised of the potential risk of dehydration in relation to gastrointestinal adverse reactions and take precautions to avoid fluid depletion.

Aspiration in association with general anaesthesia or deep sedation

Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying (see section 4.8) should be considered prior to performing procedures with general anaesthesia or deep sedation.

Hyperglycaemia

The incidence of hyperglycaemic events was increased for Kyinsu compared to insulin glargine combined with insulin aspart (4.1% vs. 1.2%) and to insulin icodec (4.2% vs. 2.6%), respectively. For Kyinsu, most of the hyperglycaemic events were reported during the first 12 weeks of treatment. In patients who were previously treated with higher pre-study daily basal insulin doses (≥ 40 U) and had higher baseline glycated haemoglobin A_{1c} (HbA_{1c}) (≥ 8.5%), fasting plasma glucose increased up to 3 mmol/L within the first two weeks after initiating Kyinsu, after which these values started to decrease, returning to baseline values at week 7-9 and reached glycaemic target (< 7.2 mmol/L) at week 14-17. During treatment initiation, patient's blood glucose value should be closely monitored. Initial increases in fasting plasma glucose will resolve after continuous titration (see section 4.2).

Inadequate dosing and/or discontinuation of antidiabetic medicinal products may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Furthermore, concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased requirement for antidiabetic treatment.

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, loss of appetite as well as acetone odour of breath. Untreated hyperglycaemia may eventually lead to diabetic ketoacidosis, which is potentially lethal. Administration of rapid-acting insulin should be considered in situations of severe hyperglycaemia.

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists, including semaglutide (see section 4.8). Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Kyinsu should be discontinued; if confirmed, Kyinsu should not be restarted. Caution should be exercised when treating patients with a history of pancreatitis.

Diabetic retinopathy

In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has previously been observed. Patients with medical history of diabetic retinopathy should therefore be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy (see section 4.8), but other mechanisms cannot be excluded. There is no experience with Kyinsu in patients with uncontrolled and potentially unstable diabetic retinopathy or maculopathy and Kyinsu is therefore not recommended in these patients.

For subjects without diabetes retinopathy at baseline see section 4.8.

Hypersensitivity reactions

Immediate-type allergic reactions to either insulin icodec or semaglutide may potentially be life-threatening.

In Kyinsu clinical studies, hypersensitivity reactions have been reported in patients treated with Kyinsu (see section 4.8).

Lipodystrophy and cutaneous amyloidosis (injection site reactions)

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis (see section 4.8). There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these adverse 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 medicinal products may be considered.

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 congestive heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Kyinsu is considered. If the combination is used, patients should be observed for signs and symptoms of congestive heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Avoidance of medication errors

Patients must be instructed to always check the label on the pre-filled pen before each injection to avoid accidental mix-ups between Kyinsu and other injectable diabetes medicinal products.

Patients must visually verify the dialled dose steps on the dose counter of the pre-filled 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 pre-filled pen.

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 at the end of the package leaflet.

Switch from other injectable diabetes treatment to weekly Kyinsu

During switch from other injectable diabetes treatment, medication errors can occur in the form of e.g. overdose or dosing errors. These errors could result in hypoglycaemia, hyperglycaemia or gastrointestinal adverse reactions. Patients switching from a daily or other once-weekly injectable diabetes treatment must be instructed to check that they inject the correct prescribed dose on a once-weekly basis. Patients who are uncertain about the correct dose must be instructed to consult their healthcare professional for further guidance.

Immunogenicity

Administration of Kyinsu may cause formation of antibodies against insulin icodec and/or semaglutide. In rare cases, the presence of such antibodies may necessitate adjustment of the Kyinsu dose to correct a tendency for hyperglycaemia or hypoglycaemia (see sections 5.1 and 5.2).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical studies on potential drug, food or alcohol interactions have been performed for Kyinsu. Interactions with other medicinal products identified with the use of the mono-components insulin icodec and semaglutide, are presented below.

Insulin icodec

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

Substances that may reduce the insulin requirement

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

Substances that may increase the insulin requirement

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

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

Beta-blockers may mask the symptoms of hypoglycaemia.

Semaglutide

Semaglutide may delay gastric emptying and could potentially influence the absorption of concomitantly administered oral medicinal products. The potential effect of semaglutide on the absorption of co-administered oral medicinal products was studied for semaglutide 1 mg at steady state exposure.

No clinically relevant drug-drug interactions with semaglutide were observed based on the evaluated medicinal products (warfarin and other coumarin derivatives, paracetamol, oral contraceptives, atorvastatin, digoxin and metformin). Therefore, no dose adjustment is required when these medicinal products are co-administered with semaglutide.

- Warfarin and other coumarin derivates: Upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of international normalised ratio (INR) is recommended. Semaglutide did not change the overall exposure or C_{max} of R- and S-warfarin following a single dose of warfarin (25 mg), and the pharmacodynamic effects of warfarin as measured by the international normalised ratio (INR) were not affected in a clinically relevant manner. However, cases of decreased INR have been reported during concomitant use of acenocoumarol and semaglutide.

- Paracetamol: Semaglutide delays the rate of gastric emptying as assessed by paracetamol pharmacokinetics during a standardised meal test. Paracetamol $AUC_{0\text{-}60min}$ and C_{max} were decreased by 27% and 23%, respectively, following concomitant use of semaglutide 1 mg. The total paracetamol exposure ($AUC_{0\text{-}5h}$) was not affected. No clinically relevant effect on paracetamol was observed with semaglutide. No dose adjustment of paracetamol is necessary when administered with semaglutide.

- Oral contraceptives: Semaglutide is not anticipated to decrease the effectiveness of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20% was observed for levonorgestrel exposure at steady state. C_{max} was not affected for any of the compounds.

- Atorvastatin: Semaglutide did not change the overall exposure of atorvastatin following a single dose administration of atorvastatin (40 mg). Atorvastatin C_{max} was decreased by 38%. This was assessed not to be clinically relevant.

- Digoxin: Semaglutide did not change the overall exposure or C_{max} of digoxin following a single dose of digoxin (0.5 mg).

- Metformin: Semaglutide did not change the overall exposure or C_{max} of metformin following dosing of 500 mg twice daily over 3.5 days.

4.6 Fertility, pregnancy and lactation

There is no available information about fertility, pregnancy and lactation for Kyinsu.
The warnings and precaution identified for the mono-components are presented below.

Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 2 months after treatment with Kyinsu.

Pregnancy

There is no clinical experience with the use of insulin icodec in pregnant women. Animal reproduction studies with insulin icodec have not revealed any effects regarding embryotoxicity and teratogenicity.

There are limited data from the use of semaglutide in pregnant women. Animal reproduction studies with semaglutide have shown reproductive toxicity (see section 5.3).

Therefore, due to the animal findings for semaglutide and limited clinical experience, Kyinsu should not be used during pregnancy.

If a patient wishes to become pregnant, or pregnancy occurs, Kyinsu should be discontinued.
Kyinsu should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2).

Breast-feeding

It is unknown whether insulin icodec is excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of insulin icodec in milk. A risk to the newborns/infants cannot be excluded.

In lactating rats, semaglutide was excreted in milk. A risk to a breast-fed child cannot be excluded.

Therefore, due to the finding in lactating rats for mono-components, Kyinsu should not be used during breast-feeding.

Fertility

The effect of insulin icodec on fertility in humans is unknown. Animal reproduction studies with insulin icodec have not revealed any adverse effects on fertility.

The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss (see section 5.3).

4.7 Effects on ability to drive and use machines

Kyinsu has no or negligible influence on the ability to drive or use machines.

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. 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 safety profile

Overall, the safety profile for insulin icodec/semaglutide is consistent with the safety profile of the mono-components. The most frequently reported adverse reactions during treatment with insulin icodec/semaglutide are hypoglycaemia and gastrointestinal adverse reactions including 20.1% nausea and 13.8% diarrhoea (see section 'Description of selected adverse reactions').

Tabulated list of adverse reactions

The clinical development programme of insulin icodec/semaglutide included 1 325 patients treated with insulin icodec/semaglutide from phase 3a clinical studies each of 52 weeks duration.

Adverse reactions associated with insulin icodec/semaglutide obtained from clinical studies are tabulated below. The adverse reactions are coded to preferred terms (PTs) under the MedDRA system organ class (SOC) and are presented by frequency based on phase 3a clinical studies. The frequency of the adverse reactions is expressed according to the following categories: 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions

MedDRA system organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Not known**
Immune system disorders		Hypersensitivity[1]		Anaphylactic reaction[7]	
Metabolism and nutrition disorders	Hypoglycaemia	Decreased appetite			
Nervous system disorders		Headache Dizziness	Dysgeusia		
Eye disorders		Diabetic retinopathy complications[2]			
Cardiac disorders		Heart rate increased[3]			

MedDRA system organ class	Very common	Common	Uncommon	Rare	Not known
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain[4] Abdominal distention Constipation Dyspepsia Gastritis Gastroesophageal reflux disease (GERD) Eructation Flatulence	Acute pancreatitis Delayed gastric emptying[7]		Intestinal obstruction[8]
Hepatobiliary disorders			Cholelithiasis		
Skin and subcutaneous tissue disorders				Lipodystrophy Cutaneous amyloidosis	Angioedema[8]
General disorders and administration site conditions		Fatigue	Injection site reaction[5] Peripheral oedema[6]		
Investigations		Increased lipase[7] Increased amylase[7]			

[1]Grouped term covering adverse reactions related to hypersensitivity reactions such as rash.
[2]Grouped term covering adverse reactions related to diabetic retinopathy.
[3]Grouped term covering adverse reactions related to heart rate increased.
[4]Grouped term covering adverse reactions related to abdominal pain.
[5]Grouped term covering adverse reactions related to injection site reactions.
[6]Grouped term covering adverse reactions related to peripheral oedema.
[7]Adverse reactions observed in phase 3a studies with monotherapy with subcutaneous semaglutide.
[8]From post-marketing adverse reaction reports of monotherapy with subcutaneous semaglutide.

Description of selected adverse reactions

Hypoglycaemia

In phase 3a clinical studies with insulin icodec/semaglutide, severe hypoglycaemia was defined as hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery and clinically significant hypoglycaemia was defined as plasma glucose value less than 54 mg/dL (3.0 mmol/L).

In patients with type 2 diabetes mellitus previously treated with basal insulin, the proportion of patients reporting severe or clinically significant hypoglycaemic episodes was 7.1% vs. 20.8% (insulin icodec/semaglutide vs. insulin icodec) and 10.0% vs. 58.5% (insulin icodec/semaglutide vs. basal-bolus insulin regimen). In patients with type 2 diabetes mellitus previously treated with GLP-1 receptor agonists the proportion of patients reporting severe or clinically significant hypoglycaemic episodes was 3.5% vs. 3.8% (insulin icodec/semaglutide vs. subcutaneous semaglutide).

In patients with type 2 diabetes mellitus previously treated with basal insulin, the estimated rate of severe or clinically significant hypoglycaemic episodes per patient years of exposure (PYE) was 0.153 vs. 0.68 (insulin icodec/semaglutide vs. insulin icodec) and 0.257 vs. 2.18 (insulin icodec/semaglutide vs. basal-bolus insulin regimen). In patients with type 2 diabetes mellitus

previously treated with GLP-1 receptor agonists, the estimated rate of severe or clinically significant hypoglycaemic episodes per PYE was 0.04 vs. 0.033 (insulin icodec/semaglutide vs. subcutaneous semaglutide).

Gastrointestinal adverse reactions

In phase 3a clinical studies nausea occurred in 20.1%, diarrhoea in 13.8%, vomiting in 9.1% of patients when treated with insulin icodec/semaglutide.

In patients previously treated with GLP-1 receptor agonists, the proportion of patients reporting nausea was 11.7% with insulin icodec/semaglutide compared to 11.5% with subcutaneous semaglutide, diarrhoea was 11.1% vs. 12.4%, and vomiting was 5.3% vs. 6.5% respectively. In patients with type 2 diabetes mellitus previously treated with basal insulin, the proportion of patients reporting nausea was 23.8% with insulin icodec/semaglutide compared to 3.9% with insulin icodec, diarrhoea was 15.8% vs. 7.3%, and vomiting was 10.6% vs. 2.6%, respectively. The proportion of patients reporting nausea was 21.8% with insulin icodec/semaglutide compared to 2.4% with a basal-bolus insulin regimen, diarrhoea was 12.6% vs. 5.5%, and vomiting was 10.0% vs. 2.7%, respectively.

Most events were mild to moderate in severity with median duration 2-4 days and the reporting of events decreased over time. The adverse reactions led to treatment discontinuation in 2.5%, interruptions in 1.7% and reduced dose in 4.2% of patients.

Diabetic retinopathy complications

A 2-year clinical study with subcutaneous semaglutide investigated 3 297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this study, adjudicated events of diabetic retinopathy complications occurred in more patients treated with subcutaneous semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the study.

In the phase 3a insulin icodec/semaglutide studies with 52 weeks treatment duration involving 2 637 patients with long duration of type 2 diabetes mellitus, adverse events related to diabetic retinopathy were reported in 9.3% of participants treated with insulin icodec/semaglutide and 8.1% of participants treated with comparators. In participants without diabetic retinopathy at baseline, events of diabetic retinopathy at week 52 were observed in 5.2% in the insulin icodec/semaglutide group and 3.8% in the comparator group. Most of the events were mild or moderate with no signs/symptoms were detected at the end of study eye examination.

Skin and subcutaneous tissue disorders

Lipodystrophy (including lipohypertrophy, 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).

Heart rate increased

Increased heart rate has been observed with GLP-1 receptor agonists. In the semaglutide naïve population in two of the phase 3a studies, the estimated mean changes in pulse with insulin icodec/semaglutide were 1.59 bpm vs. -0.12 bpm (insulin icodec/semaglutide vs. insulin icodec) respectively and 1.11 bpm vs. 0.67 bpm (insulin icodec/semaglutide vs. basal-bolus insulin regimen). The phase 3a study comparing insulin icodec/semaglutide with semaglutide showed an estimated mean change in pulse of -1.11 bpm for insulin icodec/semaglutide and -0.40 bpm for semaglutide.

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

Hypoglycaemia and gastrointestinal adverse reactions may develop if a patient is dosed with more Kyinsu than required.

Hypoglycaemia may develop over sequential stages:

- 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 sugar-containing products.
- Severe hypoglycaemic episodes, where the patient is not able to treat him or herself, can be treated with glucagon given intramuscularly, subcutaneously, or intranasally 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.

In case of gastrointestinal adverse reactions, appropriate treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for gastrointestinal symptoms may be necessary, considering the long half-life of semaglutide of approximately 1 week.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, long-acting, ATC code: A10AE57

Mechanism of action

Insulin icodec/semaglutide combines two active substances with complementary mechanisms of action to improve glycaemic control: insulin icodec, a basal insulin analogue, and semaglutide, a GLP-1 receptor agonist.

Insulin icodec

A slow and steady glucose-lowering effect of insulin icodec is driven by albumin binding as well as reduced insulin receptor binding and clearance. The extended half-life of insulin icodec reflects a depot of insulin icodec in the circulation and in the interstitial compartment, from which insulin icodec is slowly and continuously released and binds specifically to the insulin receptor. When insulin icodec binds to the human insulin receptor it results in the same pharmacological effects as human insulin.

The primary action of insulin, including insulin icodec, is to regulate glucose metabolism. Insulin and its analogues lower blood glucose by activating specific insulin receptors to stimulate peripheral glucose uptake, especially by skeletal muscle and fat as well as to inhibit hepatic glucose production. Insulin also inhibits lipolysis and proteolysis and enhances protein synthesis.

Semaglutide

Semaglutide is a GLP-1 analogue with 94% sequence similarity to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

GLP-1 is a physiological hormone that has multiple actions in glucose and appetite regulation, and in the cardiovascular system. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain.

Semaglutide reduces blood glucose in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.

Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high-fat foods.

GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys. The mechanism of action of semaglutide is likely multifactorial. Indirect effects are indicated by the beneficial effect of semaglutide on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies but direct effects are likely also involved. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.
Clinical data showed that semaglutide lowered albuminuria in patients with kidney disease.

Pharmacodynamic effects

Insulin icodec/semaglutide

The impact of the combination of insulin icodec and semaglutide on the pharmacodynamics of insulin icodec/semaglutide has not been studied in a clinical pharmacology study.

Clinical efficacy and safety

The safety and efficacy of insulin icodec/semaglutide were evaluated in three multinational, randomised, active-controlled, parallel-group phase 3 clinical studies. In the three clinical studies (COMBINE 1-3), the primary objective was the assessment of glycaemic control measured by change in the HbA_{1c} from baseline to week 52. These studies were conducted with different populations of patients with type 2 diabetes mellitus, defined by their previous antidiabetic treatment. Comparator treatments comprised once weekly insulin icodec (COMBINE 1), subcutaneous semaglutide 1 mg (COMBINE 2) and a basal-bolus regimen consisting of insulin glargine 100 units/mL and insulin aspart (COMBINE 3).

In all phase 3a clinical studies, the starting dose of insulin icodec/semaglutide was 40 dose steps (corresponding to 40 units of insulin icodec and 0.114 mg of semaglutide), and the doses were titrated once weekly with +/- 10 dose steps following a titration regimen (see Table 2).

Table 2: Titration regimen of insulin icodec/semaglutide in COMBINE 1-3

Fasting plasma glucose			**Dose adjustment**
Value to use	**mmol/L**	**mg/dL**	**Dose steps**
Lowest of fasting plasma glucose	< 4.4	< 80	-10
Mean of fasting plasma glucose	4.4-7.2	80-130	0
	> 7.2	> 130	+10

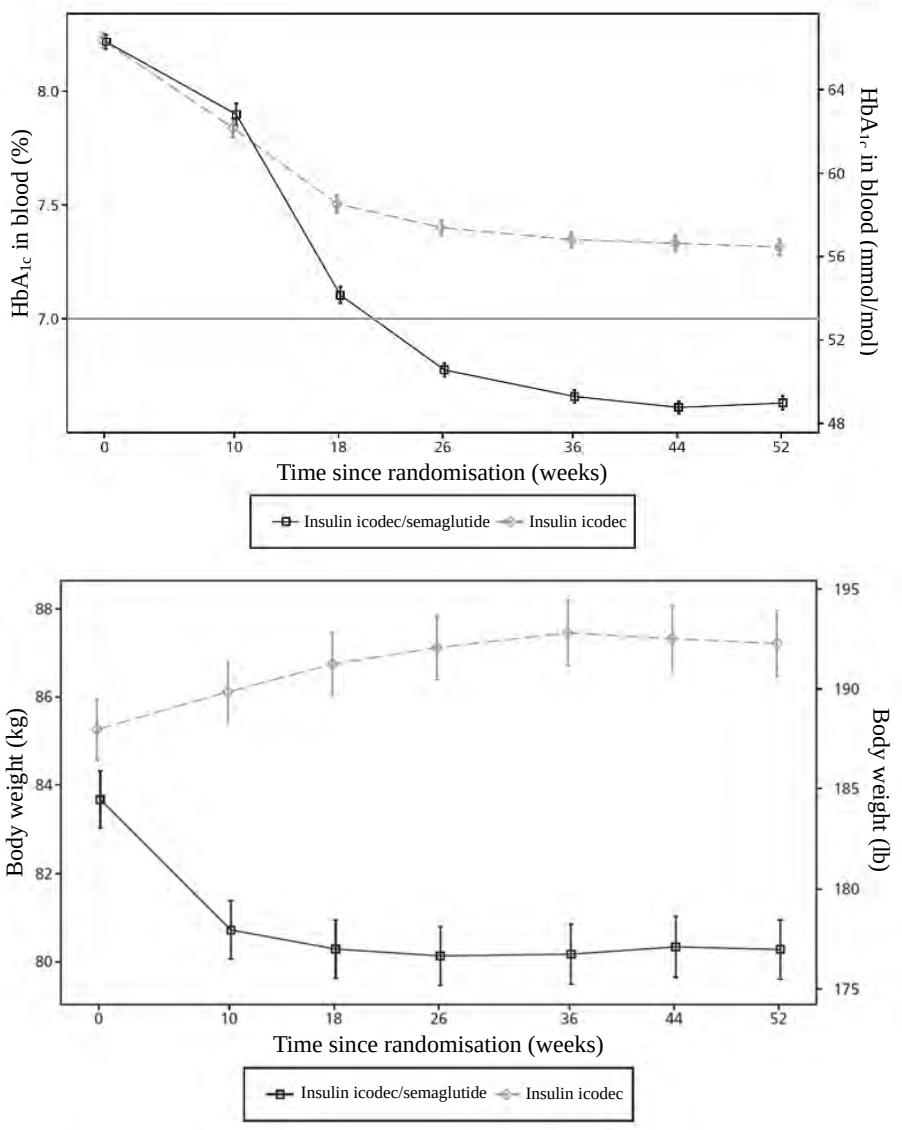
In the phase 3 clinical studies the dose adjustment was based on the mean of three pre-breakfast self-measured plasma glucose (SMPG) values measured on the day of titration and the two prior days.

The phase 3 clinical studies with type 2 diabetes mellitus patients allowed the maintenance of current non-insulin anti-diabetic treatment at the same dose level, except for glinides, sulfonylureas and DPP-4 inhibitors which were discontinued.

Switch from basal insulin: insulin icodec/semaglutide compared to once weekly basal insulin icodec (Study 4591- COMBINE 1)

A 52-week randomised, open-label clinical study was conducted with patients with type 2 diabetes mellitus insufficiently controlled on basal insulin, who were randomised to insulin icodec/semaglutide or insulin icodec, all with (93.6%) or without (6.4%) oral antidiabetics. At baseline the patients had a mean duration of diabetes of 15.34 years, a mean HbA_{1c} of 8.22%, and a mean BMI of 29.90 kg/m^2.

The key results of the study are shown in Figure 1 and Table 3.



Mean (symbol) ± standard error to mean (error bars).

Figure 1 Mean change in HbA_{1c} by treatment week (top) and body weight by treatment week (bottom) – COMBINE 1

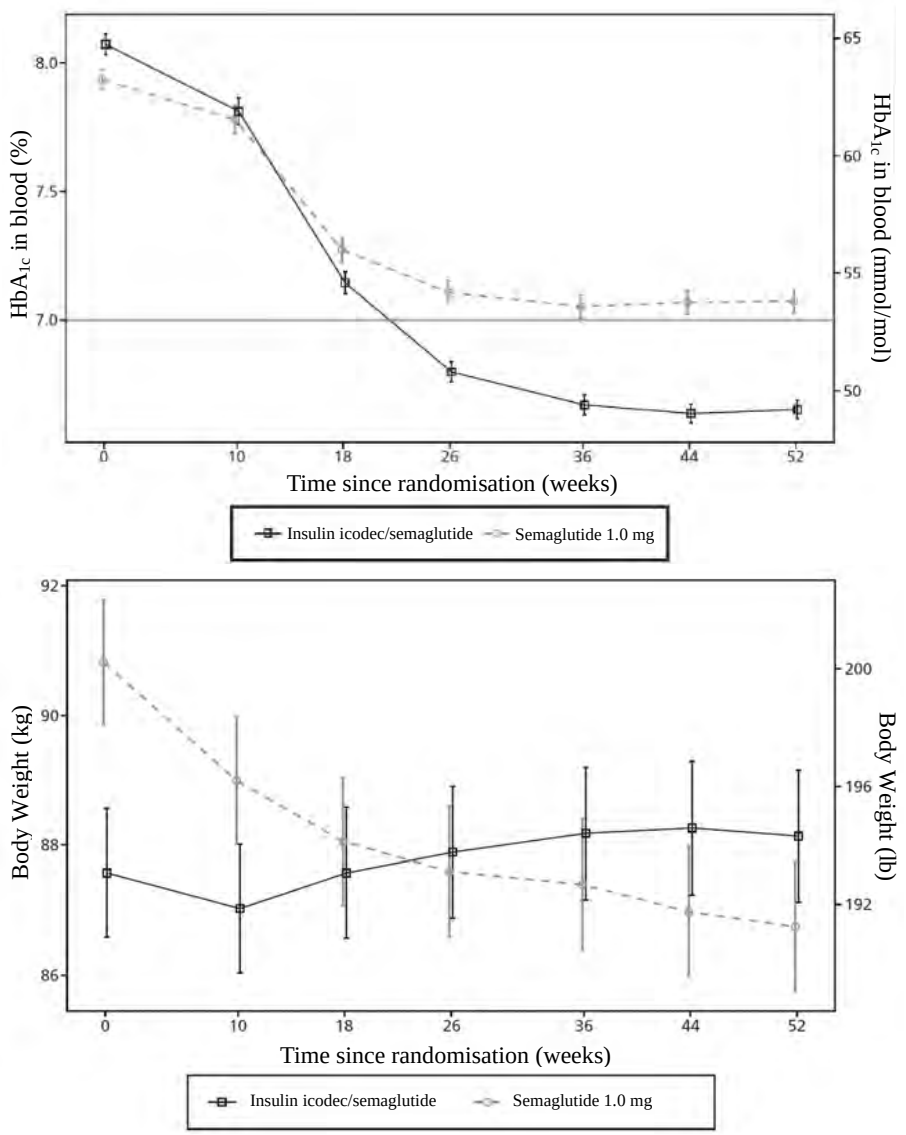
Table 3 Results from open-label (52-weeks) clinical study comparing once weekly insulin icodec/semaglutide with once weekly insulin icodec in participants with type 2 diabetes mellitus insufficiently controlled with daily basal insulin – COMBINE 1

	Insulin icodec/semaglutide	**Insulin icodec**
N (Full Analysis Set)	646	645
HbA_{1c} (%)		
Baseline (mean)	8.22	8.22
End of study*	6.67	7.33
Change from baseline at week 52*	-1.55	-0.89
Estimated difference [95% CI]	-0.66 [-0.76; -0.57][a]	
Patients (%) achieving HbA_{1c} targets		
< 7% without level 2 or 3 hypoglycaemia and without body weight gain	55.7	10.2
Estimated odds ratio [95% CI]	11.1 [8.22; 15.1][b]	
Fasting plasma glucose (FPG) (mmol/L)		
End of study*	6.92	7.06
Change from baseline at week 52*	-1.68	-1.54
Estimated difference [95% CI]	-0.14 [-0.38;0.10][b]	
Time in range 3.9-10.0 mmol/L (70-180 mg/dL) (%)		
Weeks 48-52*	73.3	61.8
Estimated difference [95% CI]	11.5 [9.35; 13.7][b, c]	
Body weight (kg)		
Baseline (mean)	83.67	85.26
Change from baseline at week 52*	-3.70	1.89
Estimated difference [95% CI]	-5.59 [-6.14; -5.04][a]	
Rates of hypoglycaemic episodes per PYE*		
Level 2 or level 3 (% of patients*)	7.1	20.8
Rate of hypoglycaemia	0.153	0.68
Estimated rate ratio [95% CI]	0.22 [0.14; 0.36][a]	
Weekly basal insulin dose (U)		
Week 50-52 (mean)*	182	355
Estimated difference [95% CI]	-172 [-190; -155][b]	

PYE = patient years of exposure
*Least Squares (LS) mean
[a] Controlled for multiplicity.
[b] Not controlled for multiplicity.
[c] 11.5% corresponds to approximately 166 minutes more spent within range per day.

Switch from GLP-1 receptor agonist: insulin icodec/semaglutide compared to GLP-1 receptor agonist (Study 4592-COMBINE 2)

In a 52-week randomised, open-label clinical study, the safety and efficacy of insulin icodec/semaglutide was compared to once-weekly semaglutide in patients with type 2 diabetes mellitus who had inadequate glycaemic control on a GLP-1 receptor agonist. The study evaluated the effectiveness of both treatments with (95.6%) or without (4.4%) oral antidiabetics. At baseline the patients had a mean duration of diabetes of 12.64 years, a mean HbA_{1c} of 8.0%, and a mean BMI of 31.11 kg/m^2.



Mean (symbol) ± standard error to mean (error bars).

Figure 2 Mean change in HbA_{1c} by treatment week (top) and body weight by treatment week (bottom) – COMBINE 2

Table 4 Results from open-label (52-weeks) clinical study comparing once weekly insulin icodec/semaglutide with once weekly semaglutide in participants with type 2 diabetes mellitus insufficiently controlled with a GLP-1 receptor agonist – COMBINE 2

	Insulin icodec/semaglutide	**Semaglutide 1 mg**
N (Full Analysis Set)	342	341
HbA_{1c} (%)		
Baseline (mean)	8.07	7.93
End of study*	6.65	7.10
Change from baseline at week 52*	-1.35	-0.90
Estimated difference [95% CI]	-0.44 [-0.56; -0.33][a]	
Patients (%) achieving HbA_{1c} targets		
< 7% without level 2 or 3 hypoglycaemia and without body weight gain at week 52*	30.2	40.5
Estimated odds ratio [95% CI]	0.64 [0.46; 0.88][b]	
Fasting plasma glucose (FPG) (mmol/L)		

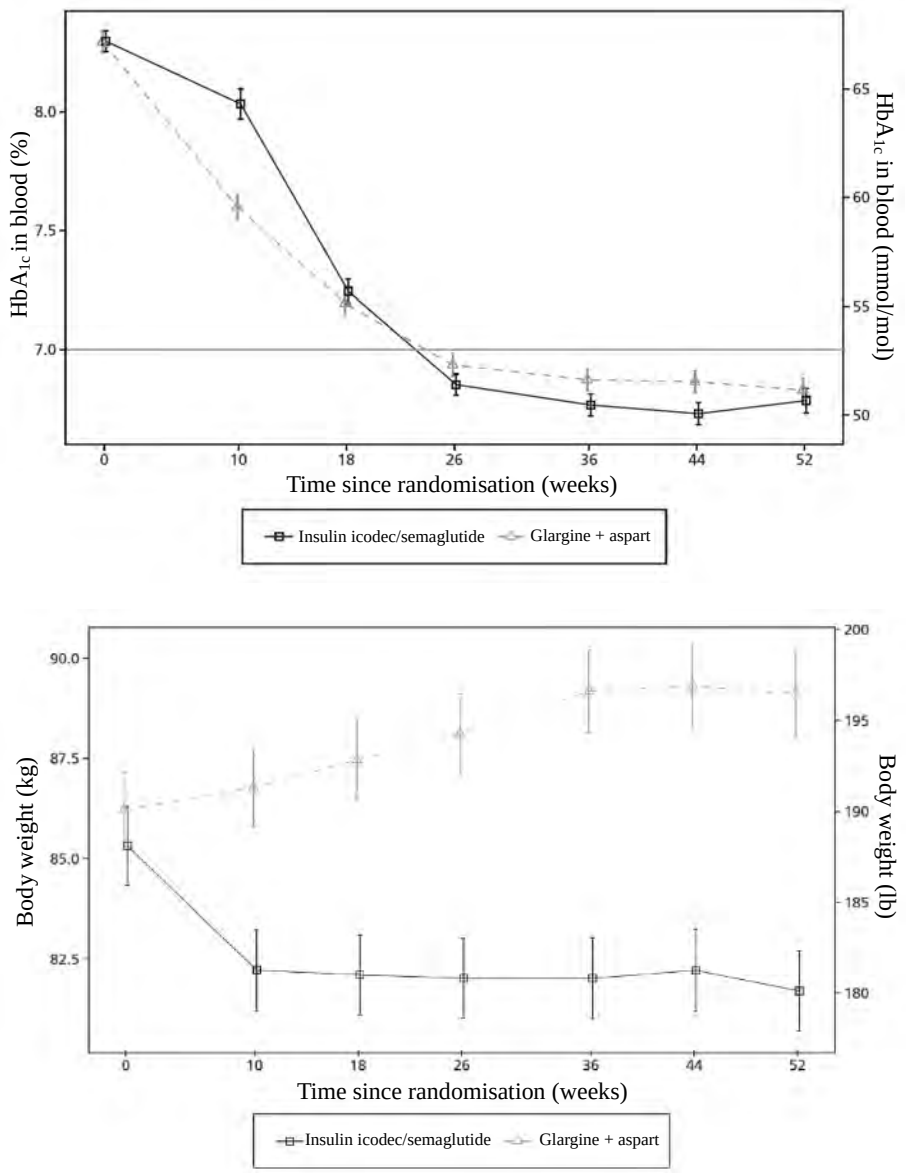
	Insulin icodec/semaglutide	Semaglutide 1 mg
End of study*	6.98	8.05
Change from baseline*	-2.48	-1.41
Estimated difference [95% CI]	-1.07 [-1.37; -0.76][b]	
Body weight (kg)		
Baseline (mean)	87.58	90.82
Change from baseline at week 52*	0.84	-3.70
Estimated difference [95% CI]	4.54 [3.84; 5.23][b]	
Rates of hypoglycaemic episodes per PYE*		
Level 2 or level 3 (% of patients*)	3.5	3.8
Rate of hypoglycaemia	0.0399	0.0334
Estimated rate ratio [95% CI]	1.20 [0.53; 2.69][b]	

PYE = patient years of exposure.
* Least Squares (LS) mean
[a] Controlled for multiplicity.
[b] Not controlled for multiplicity.

Switch from insulin regimen including basal insulin: insulin icodec/semaglutide compared to a basal-bolus regimen (Study 4593- COMBINE 3)

A 52-week randomised, open-label clinical study was conducted with patients with type 2 diabetes mellitus insufficiently controlled on basal insulin, who were randomised to insulin icodec/semaglutide or basal-bolus insulin regimen, all with (95.3%) or without (4.7%) oral antidiabetics. The basal-bolus insulin regimen consisted of daily basal insulin (insulin glargine 100 units/mL) in combination with bolus insulin (insulin aspart). At baseline the patients had a mean duration of diabetes of 14.42 years, a mean HbA_{1c} of 8.30%, and a mean BMI of 30.39 kg/m^2.

The key results of the study are shown in Figure 3 and Table 5.



Mean (symbol) ± standard error to mean (error bars).

Figure 3 Mean change in HbA_{1c} by treatment week (top) and body weight by treatment week (bottom) – COMBINE 3

Table 5 Results from open-label (52-weeks) clinical study comparing once weekly insulin icodec/semaglutide with daily insulin glargine combined with insulin aspart in participants with type 2 diabetes mellitus insufficiently controlled with daily basal insulin – COMBINE 3

	Insulin icodec/semaglutide	**Basal-bolus insulin regimen**
N (Full Analysis Set)	340	339
HbA_{1c} (%)		
Baseline (mean)	8.30	8.29
End of study*	6.83	6.89
Change from baseline at week 52*	-1.47	-1.40
Estimated difference [95% CI]	-0.06 [-0.22; 0.09][a]	
Patients (%) achieving HbA_{1c} targets		
< 7% without level 2 or 3 hypoglycaemia and without body weight gain*	50.1	5.95
Estimated odds ratio [95% CI]	15.9 [9.75; 25.8][c]	

	Insulin icodec/semaglutide	Basal-bolus insulin regimen
Fasting plasma glucose (FPG) (mmol/L)		
End of study*	7.12	7.10
Change from baseline at week 52*	-1.56	-1.58
Estimated difference [95% CI]	0.02 [-0.34; 0.38][c]	
Time in range 3.9-10.0 mmol/L (70-180 mg/dL) (%)		
Weeks 48-52*	68.6	66.4
Estimated difference [95% CI]	2.21 [-0.86; 5.27][c, d]	
Body weight (kg)		
Baseline (mean)	85.32	86.22
Change from baseline at week 52*	-3.56	3.16
Estimated difference [95% CI]	-6.72 [-7.58; -5.86][b]	
Rates of hypoglycaemic episodes per PYE*		
Level 2 or level 3 (% of patients*)	10.0	58.5
Rate of hypoglycaemia	0.257	2.18
Estimated rate ratio [95% CI]	0.12 [0.08; 0.17][b]	
Weekly insulin dose (total) (U)		
Week 50-52 (mean)*	196	466[e]
Estimated difference [95% CI]	-270 [-303; -236][b]	

PYE = patient years of exposure.
* Least Squares (LS) mean
[a] Controlled for multiplicity. The non-inferiority margin 0.3%-point.
[b] Controlled for multiplicity.
[c] Not controlled for multiplicity.
[d] 2.21% corresponds to approximately 31 minutes more spent within range per day.
[e] Total weekly insulin dose for the comparator included bolus and basal insulin.

Cardiovascular outcomes in the SUSTAIN programme (semaglutide)

No cardiovascular outcomes clinical studies have been performed with insulin icodec/semaglutide. The effect of semaglutide, a mono-component of insulin icodec/semaglutide, on cardiovascular events in adults with type 2 diabetes mellitus who had established cardiovascular (CV) disease or were at risk for CV disease, was evaluated in the SUSTAIN 6 study (cardiovascular outcome study with once-weekly subcutaneous semaglutide).

The SUSTAIN 6 study was a 104-week placebo-controlled, double-blind study with 3 297 patients with type 2 diabetes mellitus at high cardiovascular risk. These patients were randomised to either subcutaneous semaglutide 0.5 mg once weekly, subcutaneous semaglutide 1 mg once weekly or corresponding placebo in addition to standard-of-care hereafter followed for 2 years.

The study population was distributed by age as: 1 598 patients (48.5%) ≥ 65 years, 321 (9.7%) ≥ 75 years, and 20 (0.6%) ≥ 85 years. There were 2 358 patients with normal or mild renal impairment, 832 with moderate and 107 with severe or end stage renal impairment. There were 61% males, the mean age was 65 years, and mean BMI was 33 kg/m2. The mean duration of diabetes was 13.9 years.

The primary endpoint was time from randomisation to first occurrence of a major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (Figure 4).

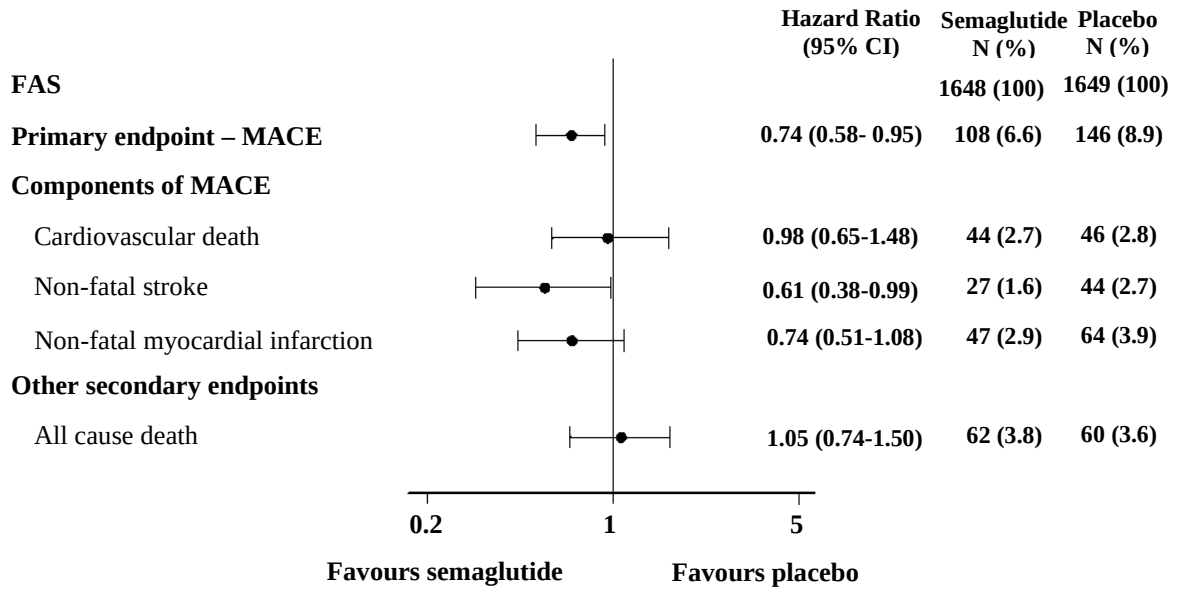


Figure 4 Forest plot: analyses of time to first occurrence of the composite outcome, its components and all cause death (SUSTAIN 6)

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with insulin icodec/semaglutide in all subsets of the paediatric population for type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

Immunogenicity

In patients with type 2 diabetes mellitus, treatment with insulin icodec/semaglutide induced anti-drug antibody (ADA) development against both subcutaneous insulin icodec and semaglutide. In previously insulin-naïve patients, 68.2% developed anti-insulin icodec antibodies (COMBINE 2). In patients previously treated with insulin, 72.5% developed anti-insulin icodec antibodies (COMBINE 1). Most of the anti-insulin icodec antibody positive patients also cross reacted with human insulin. The ADA titres peaked early after 6-10 weeks of treatment and declined thereafter.

Insulin icodec antibodies did not appear to be associated with an increased risk for injection site reactions, hypersensitivity or hypoglycaemic episodes. Due to the limited number of cases, no firm conclusions could be drawn regarding correlation between change in antibody titres from baseline and efficacy parameters. However, the 26 weeks immunogenicity findings in the clinical development programme for insulin icodec did not indicate any correlation between change in insulin icodec antibodies and efficacy parameters.

Development of anti-semaglutide antibodies when treated with insulin icodec/semaglutide occurred infrequently as just 1.4% developed anti-semaglutide antibodies mostly of a transient nature. The number of cases were too low to allow proper assessments of associations with efficacy and safety parameters. In the clinical development programme for subcutaneous semaglutide, no effect on semaglutide exposure, HbA_{1c} or semaglutide safety profile was identified and no association with immunogenicity related adverse reactions was evident.

5.2 Pharmacokinetic properties

The following reflects the pharmacokinetic properties of insulin icodec/semaglutide unless stated that the presented data is from administration of insulin icodec or semaglutide alone.

The pharmacokinetic profile of insulin icodec/semaglutide is consistent with once-weekly dosing, and clinical steady state concentration of insulin icodec and semaglutide is reached after 3-4 weeks of weekly administration.

The effect of ADA is not considered clinically relevant for semaglutide or insulin icodec pharmacokinetics.

Absorption

In clinical pharmacology studies, the total exposure (relative bioavailability) of insulin icodec and semaglutide were not affected in a clinically relevant manner when administered as insulin icodec/semaglutide compared with separate administration of insulin icodec and semaglutide.

No clinically relevant differences were observed in the estimated maximum concentration and time to maximum concentration of insulin icodec following insulin icodec/semaglutide administration and separate administration of insulin icodec.

The maximum concentration of semaglutide was higher (up to 2-fold following single-dose and estimated to 1.5-fold at steady state), and time to maximum concentration occurred earlier following insulin icodec/semaglutide administration compared to separate administration of semaglutide.

Distribution

Insulin icodec and semaglutide are extensively bound to plasma proteins (> 99% for both).

Biotransformation

Degradation of insulin icodec is similar to that of human insulin; all metabolites formed are inactive.

Semaglutide is extensively metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain. The enzyme neutral endopeptidase (NEP) is expected to be involved in the metabolism of semaglutide.

Elimination

Insulin icodec and semaglutide have an elimination half-life of approximately 1 week after subcutaneous administration.

In a clinical study with a single subcutaneous dose of radiolabelled semaglutide, it was found that the primary excretion routes of semaglutide-related material were via urine and faeces; approximately 2/3 of semaglutide-related material were excreted via urine and approximately 1/3 in faeces. Approximately 3% of the dose was excreted as intact semaglutide via urine. In patients with type 2 diabetes clearance of semaglutide was approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose.

Linearity/non-linearity

Insulin icodec exposure increases proportionally with the insulin icodec/semaglutide dose within the studied dose range (40-350 U). Semaglutide exposure increases approximately proportionally with the insulin icodec/semaglutide dose within the studied dose range (0.1-1 mg).

Special populations

Age, gender and ethnic origin

Age (22-87 years), gender, race (White, Black or African-American, Chinese, Japanese and other Asian) and ethnicity (Hispanic or Latino, non-Hispanic or -Latino) had no clinically relevant effect on the pharmacokinetics of insulin icodec/semaglutide based on results from a population pharmacokinetic analysis.

Renal impairment

Overall, based on population-pharmacokinetic analysis, the pharmacokinetic properties of insulin icodec and semaglutide following insulin icodec/semaglutide administration are preserved and there is no clinically relevant difference between participants with normal renal function and patients with renal impairment, although the experience in patients with end-stage renal disease is limited.

Insulin icodec
There is no difference in the pharmacokinetics of insulin icodec between healthy participants and patients with renal impairment.

Semaglutide
Renal impairment does not impact the pharmacokinetics of semaglutide in a clinically relevant manner.
This was shown with a single dose of 0.5 mg subcutaneous semaglutide for patients with different degrees of renal impairment (mild, moderate, severe or patients in dialysis) compared with participants with normal renal function. This was also shown for participants with type 2 diabetes mellitus and with renal impairment based on data from phase 3a clinical studies, although the experience in patients with end-stage renal disease was limited.

Hepatic impairment

Insulin icodec
There is no difference in the pharmacokinetics of insulin icodec between healthy participants and patients with hepatic impairment.

Semaglutide
Hepatic impairment does not have any impact on the exposure of semaglutide. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with participants with normal hepatic function in a clinical study with a single-dose of 0.5 mg subcutaneous semaglutide.

5.3 Preclinical safety data

Non-clinical data on insulin icodec/semaglutide reveal no special safety concerns for humans based on studies of repeated dose toxicity.

Insulin icodec
Non-clinical data on the mono-component insulin icodec reveal no special safety concerns for humans based on studies of safety pharmacology, repeated dose toxicity, and toxicity to reproduction. The ratio of mitogenic relative to metabolic potency for insulin icodec is comparable to that of human insulin.

Semaglutide
Non-clinical data on the mono-component semaglutide reveal no special safety concerns for humans based on studies of safety pharmacology, repeated dose toxicity or genotoxicity.

Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In 2-year carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at clinically relevant exposures. No other treatment-related tumours were observed. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low but cannot be completely excluded.

In fertility studies in rats, semaglutide did not affect mating performance or male fertility. In female rats, an increase in oestrous cycle length and a small reduction in corpora lutea (ovulations) were observed at doses associated with maternal body weight loss.

In embryo-foetal development studies in rats, semaglutide caused embryotoxicity below clinically relevant exposures. Semaglutide caused marked reductions in maternal body weight and reductions in embryonic survival and growth. In foetuses, major skeletal and visceral malformations were observed, including effects on long bones, ribs, vertebrae, tail, blood vessels and brain ventricles. Mechanistic evaluations indicated that the embryotoxicity involved a GLP-1 receptor mediated impairment of the nutrient supply to the embryo across the rat yolk sac. Due to species differences in yolk sac anatomy and function, and due to lack of GLP-1 receptor expression in the yolk sac of non-human primates, this mechanism is considered unlikely to be of relevance to humans. However, a direct effect of semaglutide on the foetus cannot be excluded.

In developmental toxicity studies in rabbits and cynomolgus monkeys, increased pregnancy loss and slightly increased incidence of foetal abnormalities were observed at clinically relevant exposures. The findings coincided with marked maternal body weight loss of up to 16%. Whether these effects are related to the decreased maternal food consumption as a direct GLP-1 effect is unknown.

Postnatal growth and development were evaluated in cynomolgus monkeys. Infants were slightly smaller at delivery but recovered during the lactation period.

In juvenile rats, semaglutide caused delayed sexual maturation in both males and females. These delays had no impact upon fertility and reproductive capacity of either sex, or on the ability of the females to maintain pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Zinc acetate
Glycerol (E 422)
Phenol
Metacresol
Sodium chloride
Sodium hydroxide (for pH adjustment) (E 524)
Hydrochloric acid (for pH adjustment) (E 507)
Water for injections

6.2 Incompatibilities

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

Kyinsu must not be added to infusion fluids.

6.3 Shelf life

3 years.

Shelf life after first opening of the pen

After first opening or if carried as a spare, the medicinal product may be stored for a maximum of:
- 6 weeks (Kyinsu (700 units + 2 mg)/mL solution for injection in pre-filled pen (0.43 mL).
- 8 weeks (Kyinsu (700 units + 2 mg)/mL solution for injection in pre-filled pen (1.5 mL and 1 mL).

Store below 30 °C.
Can be stored in a refrigerator (2 °C - 8 °C).
Keep the cap on the pen in order to protect from light.

6.4 Special precautions for storage

Before first opening

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.

After first opening or if carried as a spare

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

6.5 Nature and contents of container

0.43 mL, 1 mL or 1.5 mL solution in a cartridge (Type I glass) with a plunger (chlorobutyl) and a laminated rubber sheet (bromobutyl) contained in a pre-filled multidose disposable pen made of polypropylene, polyoxymethylene, polycarbonate-acrylonitrile butadiene styrene and acrylonitrile butadiene styrene.

The pre-filled pen is designed to be used with 30G, 31G, and 32G disposable needles up to a length of 8 mm.

The pen body is green, and the pen label is pink rose with a blue-coloured box highlighting the formulation strength. The outer packaging is pink rose with the formulation strength indicated in a blue-coloured box.

Pack sizes

Kyinsu pre-filled pen containing 300 units of insulin icodec and 0.86 mg of semaglutide in 0.43 mL solution
- 1 pre-filled pen without needles.
- 1 pre-filled pen with 6 disposable NovoFine Plus needles.

Kyinsu pre-filled pen containing 700 units of insulin icodec and 2 mg of semaglutide in 1 mL solution
- 1 pre-filled pen without needles.
- 1 pre-filled pen with 9 disposable NovoFine Plus needles.

Kyinsu pre-filled pen containing 1 050 units of insulin icodec and 3 mg of semaglutide in 1.5 mL solution
- 1 pre-filled pen without needles.
- 1 pre-filled pen with 9 disposable NovoFine Plus needles.

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.

Kyinsu must not be used if the solution does not appear clear and colourless or almost colourless.

Kyinsu must not be used if it has been frozen.

A new needle must always be attached before each injection.
Needles must not be reused. Needles must be discarded immediately after use.
In the event of blocked needles, patients must follow the instructions described in the instructions for use at the end of the package leaflet.

For detailed instructions for use, see the end of the package leaflet.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Alle 1
DK-2880 Bagsvaerd
Denmark

8. MARKETING AUTHORISATION NUMBERS

EU/1/25/1992/001
EU/1/25/1992/002
EU/1/25/1992/003
EU/1/25/1992/004
EU/1/25/1992/005
EU/1/25/1992/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

Name and address of the manufacturer of the biological active substances

Novo Nordisk A/S
Hallas Alle 1
DK-4400 Kalundborg
Denmark

Name and address of the manufacturer responsible for batch release

Novo Nordisk A/S
Novo Alle 1
DK-2880 Bagsvaerd
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 (PSURs)**

The requirements for submission of PSURs 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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (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.

- **Additional risk minimisation measures**

The MAH shall provide an education guide prior to launch targeting all patients who will be treated with Kyinsu. The educational guide is aimed at increasing awareness and describing the key points of use to minimise the risk of medication errors due to mix-up and during switch

from other injectable diabetes treatments to once-weekly Kyinsu in adults with type 2 diabetes mellitus.

The educational guide contains information and instructions related to the following key elements:

For medication error during switch from other injectable diabetes treatments:

- Instructions stating that the dose adjustment of Kyinsu is different from other inject-able diabetes treatments.
- Instructions to strictly adhere to the weekly dosing regimen as prescribed by the healthcare professional.
- Instructions to check how many dose steps were selected before injecting the weekly dose.
- Instructions to always use the dose counter and the dose pointer to select the dose. Do not count the pen clicks to select the dose.

For medication errors due to mix-up:

- Instructions to always check the product label before each injection to avoid accidental mix- ups between Kyinsu and other injectable diabetes treatments.

The MAH shall agree on the final content of the education guide together with a communication plan, with the National Competent Authority in each Member State prior to distribution of the educational guide in the Member State.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kyinsu (700 units + 2 mg)/mL solution for injection in pre-filled pen
insulin icodec/semaglutide

2. STATEMENT OF ACTIVE SUBSTANCES

1 mL solution contains 700 units of insulin icodec and 2 mg of semaglutide.

Each pre-filled pen contains 300 units of insulin icodec and 0.86 mg of semaglutide in 0.43 mL solution.
Each pre-filled pen contains 700 units of insulin icodec and 2 mg of semaglutide in 1 mL solution.
Each pre-filled pen contains 1 050 units of insulin icodec and 3 mg of semaglutide in 1.5 mL solution.

10 dose steps contain 10 units of insulin icodec and 0.029 mg of semaglutide.

3. LIST OF EXCIPIENTS

Zinc acetate, glycerol, phenol, metacresol, sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
FlexTouch

1x0.43 mL pre-filled pen
1x0.43 mL pre-filled pen with 6 disposable needles
1x1 mL pre-filled pen
1x1 mL pre-filled pen with 9 disposable needles
1x1.5 mL pre-filled pen
1x1.5 mL pre-filled pen with 9 disposable needles

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
subcutaneous use

once weekly

The pen shows dose steps.
One increment equals 10 dose steps.

Open here

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 or almost colourless solution.
For use by one person only.
Use a new needle for every injection.
Needles are not included

8. EXPIRY DATE

EXP/
After first opening: Use within 6 weeks (pre-filled pen of 0.43 mL)
After first opening: Use within 8 weeks (pre-filled pens of 1 mL and 1.5 mL)

9. SPECIAL STORAGE CONDITIONS

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

After first opening:
Store below 30 °C.
Can be stored in a refrigerator (2 °C - 8 °C).
Keep the cap on the pen in order to protect it 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 Alle 1
DK-2880 Bagsvaerd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/25/1992/001 1 pre-filled pen of 0.43 mL without needles
EU/1/25/1992/002 1 pre-filled pen of 0.43 mL with 6 disposable needles
EU/1/25/1992/003 1 pre-filled pen of 1 mL without needles
EU/1/25/1992/004 1 pre-filled pen of 1 mL with 9 disposable needles
EU/1/25/1992/005 1 pre-filled pen of 1.5 mL without needles
EU/1/25/1992/006 1 pre-filled pen of 1.5 mL with 9 disposable needles

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kyinsu

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

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Kyinsu (700 units + 2 mg)/mL solution for injection
insulin icodec/semaglutide
FlexTouch
SC

2. METHOD OF ADMINISTRATION

subcutaneous use
once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.43 mL
1 mL
1.5 mL

6. OTHER

Novo Nordisk A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kyinsu (700 units + 2 mg)/mL solution for injection in pre-filled pen
insulin icodec/semaglutide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 Kyinsu is and what it is used for

Kyinsu is a diabetes medicine containing two active substances:
- Insulin icodec: a replacement insulin that acts in the same way as naturally produced insulin, but works for a longer time. It helps to control the amount of blood sugar in your body.
- Semaglutide: a substance that acts like the hormone GLP-1 in your body. It reduces your blood sugar level when it is too high.

Kyinsu is used to control high blood sugar levels in adults with type 2 diabetes who are not controlled on basal insulin or glucagon-like peptide 1 (GLP-1). Kyinsu is used together with diet, exercise and oral (taken by mouth) medicines to treat diabetes.

2. What you need to know before you use Kyinsu

Do not use Kyinsu
- if you are allergic to insulin icodec, semaglutide 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** Kyinsu if:
- you have type 1 diabetes - a condition where your body does not produce enough insulin.
- you have diabetic ketoacidosis - a complication of diabetes causing excess acid in the blood.
- you have low blood sugar. This may occur when your dose of Kyinsu is too high, if you miss a meal, or if you did any unplanned and strenuous physical exercise - follow the advice at the end of this leaflet under ‘Too low blood sugar (hypoglycaemia)’.
- you have high blood sugar - follow the advice at the end of this leaflet under ‘Too high blood sugar (hyperglycaemia)’.
- you have severe heart failure.

- you are taking pioglitazone. When pioglitazone is used together with insulin it needs special attention - see 'Other medicines and Kyinsu' below.
- you have eye problems. Sudden improvements in blood sugar control may lead to temporary worsening of diabetic eye retinopathy. This eye condition can cause loss of vision and blindness in people with diabetes. Talk to your doctor if you have eye problems.

Ensure that you use the right medicine. Always check the pen label before each injection to avoid mix-ups between Kyinsu and other medicines. Users who are blind or with poor eyesight should get help from a person with good eyesight who is trained in using the pre-filled pen.

Talk to your doctor, pharmacist or nurse **during treatment** with Kyinsu if you have:
- severe and ongoing pain in your stomach area. This could be a sign of inflamed pancreas (acute pancreatitis).
- loss of fluids from your body (dehydration) e.g. in case of vomiting and diarrhoea. It is important to drink plenty of fluids, especially during the first weeks of treatment with Kyinsu. This is especially important if you have kidney problems.
- skin changes at the injection site. The injection site should be changed regularly to help prevent changes to the fatty tissue under the skin. Such changes include skin thickening or shrinking, or lumps under the skin. Kyinsu may not work very well if you inject into a lumpy area (see section 3 'How to use Kyinsu'). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may advise to check your blood sugar more closely and adjust Kyinsu dose or other diabetes medicine.

Switching from other injectable diabetes medicines
It is important that you always check that you inject your prescribed dose when you switch from a daily or other once weekly injectable diabetes medicine to once weekly Kyinsu. Always follow your doctor's recommendation on how much medicine you should inject (see section 3). Talk to your doctor, pharmacist or nurse if you are uncertain about how to use Kyinsu.

Food or liquid getting into the lungs during anaesthesia
Some patients taking medicines like semaglutide (one of the active substances in Kyinsu) have had problems with food or liquid from their stomach getting into their lungs while under general anaesthesia or deep sedation. Tell your healthcare professional that you are taking Kyinsu before you have a procedure that requires general anaesthesia or deep sedation.

Antibodies to Kyinsu
Treatment with Kyinsu can cause the body to produce antibodies to insulin or the GLP-1 hormone. Very rarely, this may require you to change your dose of Kyinsu.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years of age. No experience exists with using Kyinsu in this age group.

Other medicines and Kyinsu
Tell your doctor, pharmacist or nurse if you are using, have recently used or might use any other medicines. Some medicines affect your blood sugar level, this may mean your dose of Kyinsu has to be changed.

If you use **basal insulin or GLP-1 receptor agonist treatment,** discuss with your doctor when you should stop the basal insulin and GLP-1 receptor agonist treatment prior to starting on Kyinsu.

Listed below are the most common medicines that may affect your treatment with Kyinsu.

You may need a lower dose of Kyinsu if you take:
- other medicines for diabetes (by mouth or injection)
- sulphonamides – for bacterial infections
- anabolic steroids (such as testosterone)

- beta-blockers – for high blood pressure, heart disease or other illnesses. These medicines may make it harder to recognise the warning signs of low blood sugar (see information in the box at the end of this leaflet under Warning signs of too low blood sugar).
- acetylsalicylic acid and medicines called 'salicylates' – for pain and mild fever
- monoamine oxidase inhibitors – for depression or Parkinson's disease
- angiotensin-converting enzyme inhibitors – for some heart problems or high blood pressure.

These medicines may cause your blood sugar levels to fall (hypoglycaemia) when you use them in combination with Kyinsu.

You may need a higher dose of Kyinsu if you take:
- danazol – medicine affecting ovulation
- oral contraceptives
- 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).

These medicines may cause your blood sugar level to rise (hyperglycaemia) when you take them together with Kyinsu.

Warfarin and other similar **medicines** taken by mouth **to reduce blood clotting**. You may need frequent blood tests to check how quickly your blood clots.

Octreotide and lanreotide – for acromegaly, a rare illness involving excess growth hormone. They may increase or decrease your blood sugar level.

Pioglitazone – a diabetes medicine given by mouth for type 2 diabetes. Some patients with long-standing type 2 diabetes, heart disease or previous stroke, developed heart failure when treated with pioglitazone and insulin. Inform your doctor immediately upon signs of heart failure, such as shortness of breath, tiredness, fluid retention, weight gain, ankle swelling.

Kyinsu with alcohol
Your blood sugar level may either rise or fall if you drink alcohol. You need to check your blood sugar level more often than usual when you drink alcohol.

Pregnancy and breast-feeding
This medicine should not be used during pregnancy, as it is not known if it affects an unborn baby. Therefore, use of effective contraception is recommended while using this medicine. If you wish to become pregnant, discuss with your doctor how to change your treatment, as you should stop using this medicine at least 2 months in advance.

It is not known if this medicine is excreted in breast milk and a risk for the baby cannot be excluded. Therefore, Kyinsu is not recommended while breast-feeding. The doctor will decide if you should stop treatment with this medicine or breast-feeding.

Driving and using machines
Kyinsu is unlikely to affect your ability to drive or use machines, but it changes your blood sugar levels. Having too low or too high blood sugar can affect your ability to drive or use machines. It may also reduce your ability to concentrate or react, which may pose a danger to you or others. Ask your doctor or nurse for guidance if:
- you often get low blood sugar
- you find it hard to recognise low blood sugar.

Kyinsu contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use Kyinsu

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

Kyinsu is given **once a week**.
- Inject Kyinsu on the same day of the week. To help you remember to inject this medicine once a week only, it is recommended to note the chosen weekday in a calendar.
- You can use the medicine at any time of the day.

How much to inject
Your doctor will decide together with you:
- how much Kyinsu you will need each week
- when to check your blood sugar level
- when you need to change your dose - your doctor may change your dose based on your blood sugar level
- if your treatment needs to be adjusted when using other medicines.

The maximum recommended weekly dose is 350 dose steps.

How Kyinsu is given
Kyinsu is a pre-filled dial-a-dose pen.
- Kyinsu 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 thighs, upper arms or your belly.
    - Change the area where you inject each time to reduce the risk of developing lumps and skin pitting (see sections 2 and 4).
    - Always use a new needle for each injection. Re-use of needles increases 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.
- Kyinsu is given in ‘dose steps’. The dose counter on the pen shows the number of dose steps.
- The pre-filled pens of Kyinsu can provide the following doses:
    - The pre-filled pen of 0.43 mL can provide from 10 to 300 dose steps in one injection, in increments of 10 dose steps.
    - The pre-filled pen of 1 mL can provide from 10 to 350 dose steps in one injection, in increments of 10 dose steps.
    - The pre-filled pen of 1.5 mL can provide from 10 to 350 dose steps in one injection, in increments of 10 dose steps.
- 10 dose steps contain 10 units of insulin icodec and 0.029 mg of semaglutide.

Always check the pen label before injecting your medicine to ensure you are using the correct pen.

If you are blind or have difficulty reading the dose counter on the pen, you must not use this pen without help. Get help from a person with good eyesight who is trained to use the pre-filled pen.

Before you use Kyinsu for the first time your doctor or nurse will show you how to inject.
Carefully read the ‘Instructions for use’ on the other side of this leaflet and use the pen as described.

Do not use Kyinsu
- in insulin infusion pumps
- if the pen is damaged or has not been stored correctly (see section 5)
- if there are visible particles - the solution should be clear and colourless.

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.

If you use more Kyinsu than you should
Your blood sugar may get low or you may have nausea or vomiting. If your blood sugar gets low, see advice at the end of this leaflet under 'Too low blood sugar (hypoglycaemia)'.

If you forget to use Kyinsu
- If it is 3 days or less after you should have injected Kyinsu, inject as soon as you remember. Then inject your next dose on your usual injection day.
- If it is more than 3 days since you should have injected Kyinsu, inject it as soon as you remember. You should inject your next dose of Kyinsu one week after you have injected the missed dose. If you wish to return to your usual injection day, you may do so in agreement with your doctor by extending the time between your next doses.

Do not use a double dose to make up for a forgotten dose.

If you stop using Kyinsu
Do not stop using Kyinsu without agreement of your doctor. If you stop using Kyinsu your blood sugar levels may increase (hyperglycaemia) and you may develop ketoacidosis. See advice at the end of this leaflet under 'Too high blood sugar (hyperglycaemia)'.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

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

Serious side effects
- **low blood sugar (hypoglycaemia)** - very common (may affect more than 1 in 10 people)
  - Low blood sugar can be very serious.
  - If your blood sugar level falls too much, you may pass out.
  - Serious low blood sugar level may cause brain damage and may be life-threatening.

  Try to increase your blood sugar level immediately if you have signs of low blood sugar (see advice under 'Too low blood sugar (hypoglycaemia)' at the end of this leaflet).
- **damage to the retina of the eyes (diabetic retinopathy complications), which may cause vision problems** - common (may affect up to 1 in 10 people)
  Tell your doctor if you get eye problems, such as changes in vision, during treatment with this medicine.
- **skin changes where the injection is given (lipodystrophy, cutaneous amyloidosis)** - rare (may affect up to 1 in 1 000 people)
  If you inject this medicine too often at the same place:
  - the skin may shrink or thicken
  - lumps under the skin may also be caused by build-up of a protein called amyloid.

  This medicine may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.
- **severe allergic reactions (anaphylactic reactions)** - rare (may affect up to 1 in 1 000 people)
  You must get immediate medical help and inform your doctor straight away if you get symptoms such as breathing problems, swelling of face, lips, tongue and/or throat with difficulty swallowing and a fast heartbeat.

Other side effects

Very common (may affect more than 1 in 10 people)
- feeling sick (nausea)
- diarrhoea

Common (may affect up to 1 in 10 people)
- hypersensitivity reactions, such as rash or itching
- reduced appetite
- headache
- dizziness
- fast heartbeat
- vomiting
- belly (abdominal) pain
- bloating (distention) of the belly
- constipation
- indigestion (dyspepsia)
- inflamed stomach (gastritis)
- reflux or heartburn ('gastroesophageal reflux disease')
- burping
- wind (flatulence)
- tiredness
- increase of pancreatic enzymes

Uncommon (may affect up to 1 in 100 people)
- change in the way food or drink tastes (dysgeusia)
- inflammation of the pancreas (acute pancreatitis)
- a delay in the emptying of the stomach
- gall stones (cholelithiasis)
- injection site reactions
- swelling due to fluid retention, especially of the ankles and feet (peripheral oedema)

Not known (frequency cannot be estimated from the available data)
- bowel (intestinal) obstruction
- swelling of face, lips, tongue and/or throat with difficulty swallowing (angioedema)

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 Kyinsu

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 opening
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.

After first opening or if carried as a spare
You can keep Kyinsu pre-filled pen at room temperature (below 30 °C) or in a refrigerator (2 °C - 8 °C) for up to:
- 6 weeks (pre-filled pen of 0.43 mL)
  or
- 8 weeks (pre-filled pens of 1 mL and 1.5 mL).

Do not use this medicine if you notice that the solution is not clear and colourless or almost colourless.

Do not use this medicine if it has been frozen.

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

This medicine is for use by one person only.

A new needle must always be attached before each injection.
Needles must not be reused. Needles must be discarded immediately after use.
In the event of blocked needles, you must follow the instructions described in the instructions for use at the end of this leaflet.

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 Kyinsu contains
- The active substances are insulin icodec and semaglutide. Each mL of solution contains 700 units of insulin icodec and 2 mg of semaglutide.
  - Kyinsu (700 units + 2 mg)/mL (0.43 mL) contains 300 units of insulin icodec and 0.86 mg of semaglutide.
  - Kyinsu (700 units + 2 mg)/mL (1 mL) contains 700 units of insulin icodec and 2 mg of semaglutide.
  - Kyinsu (700 units + 2 mg)/mL (1.5 mL) contains 1 050 units of insulin icodec and 3 mg of semaglutide.

- The other ingredients are zinc acetate, glycerol (E 422), phenol, metacresol, sodium chloride, sodium hydroxide (for pH adjustment) (E 524), hydrochloric acid (for pH adjustment) (E 507) and water for injections (see section 2 ‘Kyinsu contains sodium').

What Kyinsu looks like and contents of the pack
Kyinsu is presented as a clear and colourless or almost colourless solution for injection in a pre-filled pen.

The pre-filled pen is designed to be used with 30G, 31G, and 32G disposable needles up to a length of 8 mm.

The outer packaging is pink rose with the formulation strength indicated in a blue-coloured box. The pen body is green, the pen label is pink rose with a blue-coloured box highlighting the formulation strength.

Pack sizes
- Pack size of 1 pre-filled pen of 0.43 mL (without needles).
- Pack size of 1 pre-filled pen of 0.43 mL (with 6 disposable NovoFine Plus needles).
- Pack size of 1 pre-filled pen of 1 mL (without needles).
- Pack size of 1 pre-filled pen of 1 mL (with 9 disposable NovoFine Plus needles).
- Pack size of 1 pre-filled pen of 1.5 mL (without needles).

- Pack size of 1 pre-filled pen of 1.5 mL (with 9 disposable NovoFine Plus needles).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Novo Nordisk A/S
Novo Alle 1
2880 Bagsvaerd
Denmark

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

HYPOGLYCAEMIA AND HYPERGLYCAEMIA

General effects from diabetes treatment
Too low blood sugar (hypoglycaemia)
This may happen if you:
- drink alcohol
- use too much Kyinsu
- exercise more than usual
- eat too little or miss a meal.

Warning signs of too low blood sugar - these may come on suddenly:
- headache
- fast heartbeat
- feeling sick or very hungry
- cold sweat or cool pale skin
- short-lasting changes in your sight
- tremor or feeling nervous or worried
- feeling unusually tired, weak and sleepy
- slurred speech, feeling confused, difficulty in concentrating.

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. This is because improvement in your blood sugar may not happen straight away.
- Then 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 administration 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 glucagon, 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 glucagon
- you have had too low blood sugar a few times recently.

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

Too high blood sugar (hyperglycaemia)
This may happen if you:
- drink alcohol
- get an infection or a fever
- have not used enough Kyinsu
- eat more or exercise less than usual
- keep using less Kyinsu than you need
- forget to use your Kyinsu or stop using Kyinsu without talking to your doctor.

Warning signs of too high blood sugar - these normally appear gradually:
- feeling thirsty
- flushed or dry skin
- losing your appetite
- feeling sleepy or tired
- passing water more often
- dry mouth or fruity (acetone) breath
- 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 or blood for ketones.
- get medical help straight away.

Instructions for use

Before you begin using your needle and Kyinsu pen, **always read these instructions carefully**, and talk to your doctor, nurse or pharmacist about how to inject Kyinsu correctly.

Kyinsu is a pre-filled disposable pen containing a solution for injection of insulin icodec and semaglutide **(700 units + 2 mg)/mL.**

Kyinsu is administered as **´dose steps´.**
Your pen delivers doses in increments of 10 dose steps.
In a single injection, the pre-filled pen can deliver doses:
- from 10 dose steps equal to 10 units of insulin icodec + 0.029 mg of semaglutide
- up to 350 dose steps equal to 350 units of insulin icodec + 1 mg of semaglutide

Do not do any conversion of your dose. The dose steps dialled equal the number shown on the dose counter.

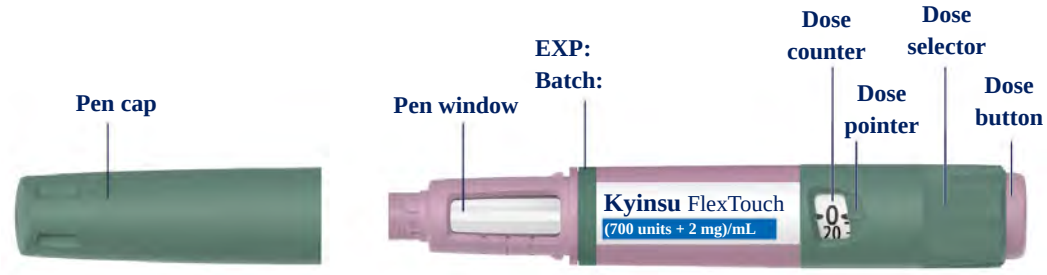
Always start by checking your pen label to make sure that it contains Kyinsu (700 units + 2 mg)/mL.

Your pen is designed to be used with 30G, 31G, and 32G disposable needles up to a length of 8 mm.

Once-weekly injection

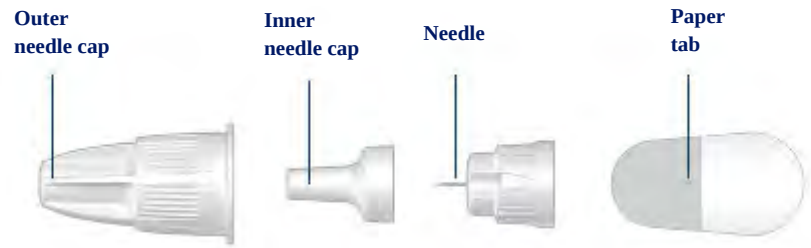
Kyinsu pen

Please note: Your pen may differ from the pen example shown in the pictures. These instructions apply to all Kyinsu pens.

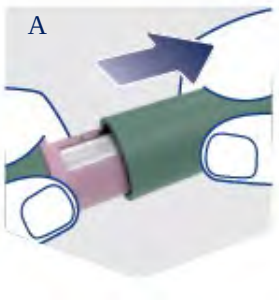
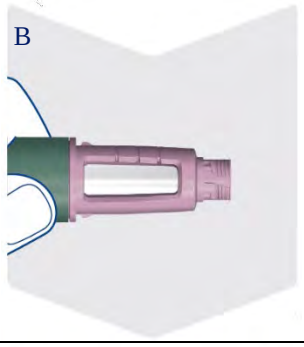
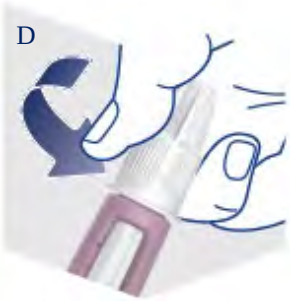


About your needles
Always use a new needle for each injection. Check the flow as described in 'Step 2' and use a new needle for each injection. Always remove the needle after each use.

NovoFine Plus Needle (example)

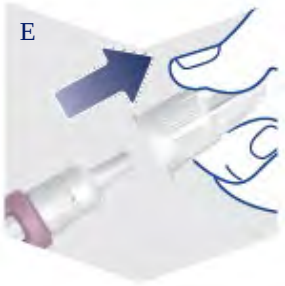


Step 1 Prepare your pen with a new needle

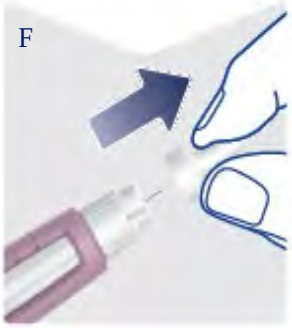
• **Check the name and concentration on the pen label** to make sure that your pen contains Kyinsu **(700 units + 2 mg)/mL.** • **Pull off the pen cap.** See Figure A.	A 
• **Always check that the solution in the pen is clear and colourless or almost colourless.** • Look through the pen window. If the solution looks cloudy or contains particles, do not use the pen. See Figure B.	B 
• **Always use a new needle for each injection.** • Check the paper tab and the outer needle cap for damages. If you see any damage, this could affect sterility. Throw out the needle and use a new one. • **Take a new needle and tear off the paper tab.** • **Do not attach a new needle to your pen until you are ready to give your injection.** See Figure C.	C 
• **Push the needle straight onto the pen. Turn until it is on tight.** See Figure D.	D 

- **The needle is covered by two caps. You must remove both caps.** If you forget to remove both caps, you will not inject any medicine.
- **Pull off the outer needle cap and keep it for later. You will need it to safely remove the needle from the pen after the injection.** See Figure E.

E



F



- **Pull off the inner needle cap and throw it away.** See Figure F.
- A drop of the solution may appear at the needle tip. This is normal, but you must still check the solution flow before each injection. See **'Step 2'.**
- **Never use a bent or damaged needle.**

Step 2 Check the flow before each injection

- **Always check the flow before each injection.** This helps you to ensure that you will get your full Kyinsu dose.
- Turn the dose selector clockwise until you see the first mark **(10 dose steps)** on the dose counter. See Figure G.

G

- Make sure that the mark lines up with the dose pointer. See Figure H.

H

- Hold the pen with the needle pointing up.
- **Press and hold in the dose button until the dose counter shows -0-.** The -0- must line up with the dose pointer.
- **A drop of the solution should appear at the needle tip.** This drop indicates that your pen is ready for use. See Figure I.
- **If a drop does not appear, check the flow again.** This should only be done six times in total.
- **If there is still no drop,** you might have a blocked needle. Change the needle as described in **'Step 5' and 'Step 1'.**
- Then, check the flow once more.
- **Do not use the pen** if a drop of the solution still does not appear.

I

Step 3 Set your dose

- Check that the dose pointer is set at -0-. See Figure J.
- Turn the dose selector to select your intended dose as directed by your nurse or doctor. The dose counter shows the dose dialled in dose steps.
- The numbers shown on the dose counter will guide you to your dose.

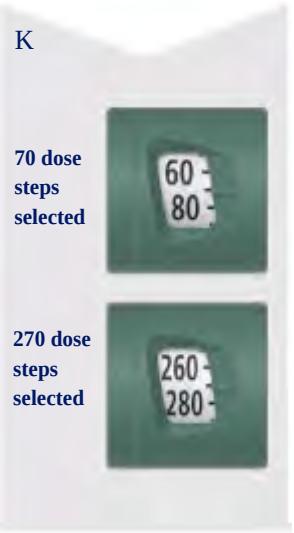
J

- **Your pen delivers doses in increments of 10 dose steps, this means that the dose can be increased by 10 dose steps at a time.**
- You may hear a 'click' every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear.
- If you select a wrong dose, you can turn the dose selector forward or backwards to the correct dose.

- When your dose lines up with the dose pointer, you have selected your dose. **Make sure you select your intended dose.**
- The pictures show examples of how to choose your dose correctly. See Figure K.

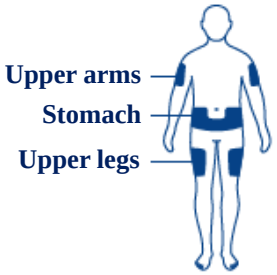
- If the dose counter stops before you reach your prescribed dose while dialling, see the section **'Do you have enough medicine?'** below these instructions.

K



Choose your injection site

- Choose an injection site on your stomach (keep a 5 cm distance from your belly button), upper legs, or upper arms.
- You may inject in the same body area each week, but make sure it is not in the same spot that was used for your last injection.



Step 4 Inject your dose

- **Fully insert the needle into your skin.** See Figure L.
- **Make sure you can see the dose counter. Do not cover the dose counter or touch it with your fingers.** This could stop the injection.

L

• **Press and hold down the dose button until the dose counter shows -0-.** • **Continue pressing the dose button with the needle in your skin and slowly count to 6.** The -0- must line up with the dose pointer. See Figure M. You may hear or feel a click when the dose counter returns to -0-.	M 
• **Remove the needle from your skin,** you can then release the dose button. See Figure N. • If the needle is removed earlier, a stream of the solution might come from the needle tip and the full dose will not be delivered. • If blood appears at the injection site, press lightly on the area to stop the bleeding. • You may see a drop of the solution at the needle tip after injecting. This is normal and does not affect your dose.	N 
Step 5 After your injection	
• **Carefully insert the needle tip into the outer needle cap on a flat surface without touching the needle or the outer needle cap.** See Figure O. • **Once the needle is covered, carefully push the outer needle cap completely on.** Not covering the needle with the outer needle cap could lead to needle stick injuries.	O 

• **Unscrew the needle** and dispose of it carefully as instructed by your doctor, nurse, pharmacist or local authorities. See Figure P. • **Never try to put the inner needle cap back on the needle.** You may stick yourself with the needle. • **Always remove and dispose of the needle immediately after each injection to prevent blocked needles, contamination, infection and inaccurate dosing.** • **Never store your pen with the needle attached.**	**P** 
• **Put the pen cap on** your pen after each use to protect the solution from light. See Figure Q. • When the pen is empty, dispose of the pen without a needle on as instructed by your doctor, nurse, pharmacist or local authorities. • The package leaflet and the empty carton can be disposed of in your household waste.	Q 
Do you have enough medicine? • **If the dose counter stops before you reach your prescribed dose while dialling,** there is not enough medicine left for a full dose. The number shown in the dose counter is the amount of medicine left in your pen. • **If you need more medicine than what is left in your pen,** you can split your dose between two pens. Be sure that you calculate correctly if you are splitting your dose. If you are in doubt, dispose of the used pen and take the full dose with a new pen. • **If you split the dose incorrectly, you will inject too little or too much medicine, which can lead to too high or too low blood sugar level.**	**Example:** **100 dose steps needed, dose counter stops at 70 dose steps.** 

⚠ Important information

- **Needles are for single-use only. Never reuse your needles** as it may lead to blocked needles, contamination, infection, leakage of medicine and inaccurate dosing.
- **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.**
- **Caregivers must be very careful when handling needles to prevent accidental needle stick injuries and infection.**
- **Do not use this pen without help if you are blind or have poor eyesight and cannot follow these instructions.** Get help from a person with good eyesight who is trained to use the Kyinsu pen.
- **Always keep pen, and needles out of sight and reach of others, especially children.**
- **Inject Kyinsu once weekly. If you do not use your Kyinsu as prescribed, this can lead to too high or too low blood sugar level.**
- **If you use more than one type of injectable medicine, it is very important to check the name and concentration of your pen label before use.**
- **Never share** your pen or your needles with other people.

Caring for your pen

- **Do not freeze Kyinsu. Do not use Kyinsu if it has been frozen. Dispose of the pen.**
- **Do not drop your pen** or knock it against hard surfaces.
- **Avoid exposing Kyinsu to direct sunlight.**
- **Keep Kyinsu away from heat, microwaves and out of the light.**
- **Do not try to repair your pen** or pull it apart.
- **Do not expose your pen to dust, dirt, or liquid.**
- **Do not wash, soak, or lubricate your pen.** It may be cleaned with a mild detergent on a moistened cloth.
- **See the back of this leaflet to read the storage conditions for your pen.**