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

Kayshild 0.25 mg solution for injection in pre-filled pen
Kayshild 0.5 mg solution for injection in pre-filled pen
Kayshild 1 mg solution for injection in pre-filled pen
Kayshild 1.7 mg solution for injection in pre-filled pen
Kayshild 2.4 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kayshild 0.25 mg solution for injection

Each pre-filled pen contains 1 mg semaglutide* in 1.5 mL solution. One mL of solution contains 0.68 mg semaglutide*. One pre-filled pen contains 4 doses of 0.25 mg.

Kayshild 0.5 mg solution for injection

Each pre-filled pen contains 2 mg semaglutide* in 3 mL solution. One mL of solution contains 0.68 mg semaglutide*. One pre-filled pen contains 4 doses of 0.5 mg.

Kayshild 1 mg solution for injection

Each pre-filled pen contains 4 mg semaglutide* in 3 mL solution. One mL of solution contains 1.34 mg semaglutide*. One pre-filled pen contains 4 doses of 1 mg.

Kayshild 1.7 mg solution for injection

Each pre-filled pen contains 6.8 mg semaglutide* in 3 mL solution. One mL of solution contains 2.27 mg semaglutide*. One pre-filled pen contains 4 doses of 1.7 mg.

Kayshild 2.4 mg solution for injection

Each pre-filled pen contains 9.6 mg semaglutide* in 3 mL solution. One mL of solution contains 3.2 mg semaglutide*. One pre-filled pen contains 4 doses of 2.4 mg.

*human glucagon-like peptide-1 (GLP-1) analogue produced in *Saccharomyces cerevisiae* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) [FlexTouch]

Clear and colourless isotonic solution; pH=7.4

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kayshild is indicated in conjunction with diet and exercise for the treatment of adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).

4.2 Posology and method of administration

Posology

The maintenance dose of semaglutide 2.4 mg once weekly is reached by starting with a dose of 0.25 mg. To reduce the likelihood of gastrointestinal symptoms, the dose should be escalated over a 16-week period to a maintenance dose of 2.4 mg once weekly (see Table 1). In case of significant gastrointestinal symptoms, consider delaying dose escalation or lowering to the previous dose until symptoms have improved. When symptoms have improved, attempt to re-escalate the dose.

Table 1 Dose escalation schedule

Dose escalation	**Weekly dose**
Week 1–4	0.25 mg
Week 5–8	0.5 mg
Week 9–12	1 mg
Week 13–16	1.7 mg
Maintenance dose	2.4 mg

Weekly doses higher than 2.4 mg are not recommended.

Patients with type 2 diabetes
When initiating semaglutide in patients with type 2 diabetes, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia, see section 4.4.

Missed dose
If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once-weekly dosing schedule. If more doses are missed, reducing the starting dose for re-initiation should be considered.

Special populations

Elderly
No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited.

Renal impairment
No dose adjustment is required for patients with mild or moderate renal impairment. Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended for use in patients with severe renal impairment (eGFR< 30 mL/min/1.73m^2) including patients with end-stage renal disease (see sections 4.4, 4.8 and 5.2).

Hepatic impairment
No dose adjustment is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Experience with the use of semaglutide in patients with severe (Child-Pugh C) hepatic impairment is limited. Semaglutide is not recommended to be initiated for use in patients with severe hepatic impairment and should be used cautiously in patients with moderate hepatic impairment

(see sections 4.4 and 5.2). In patients with MASH and preserved hepatic function the safety profile is well established (see section 4.8). There is limited experience in patients with MASH and F4c (Child-Pugh A), however with similar safety results as in studies in patients with preserved hepatic function. There is no experience in patients with MASH and moderate or severe hepatic impairment.

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

Method of administration

Subcutaneous use.

Kayshild is administered once weekly at any time of the day, with or without meals.

It is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed. It should not be administered intravenously or intramuscularly.

The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 3 days (> 72 hours). After selecting a new dosing day, once-weekly dosing should be continued.

Patients should be advised to read carefully the instructions for use included in the package leaflet before administering the medicinal product.

For further information before administration see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance 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.

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.

Gastrointestinal effects and Dehydration

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

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists (see section 4.8). Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.
In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Patients with type 2 diabetes

Semaglutide should not be used as a substitute for insulin in patients with type 2 diabetes. Semaglutide should not be used in combination with other GLP-1 receptor agonist products, as it has not been evaluated and an increased risk of adverse reactions related to overdose is considered likely.

Hypoglycaemia in patients with type 2 diabetes

Insulin and sulfonylurea are known to cause hypoglycaemia. Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with a GLP-1 receptor agonist. The addition of Kayshild in patients treated with insulin has not been evaluated.

Diabetic retinopathy in patients with type 2 diabetes

In patients with diabetic retinopathy treated with semaglutide, an increased risk of developing diabetic retinopathy complications has been observed (see section 4.8). Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Patients with diabetic retinopathy using semaglutide should be monitored closely and treated according to clinical guidelines.
There is no experience with Kayshild in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy. In these patients, treatment with Kayshild is not recommended.

Non-arteritic anterior ischemic optic neuropathy (NAION)

Data from epidemiological studies indicates an increased risk for non-arteritic anterior ischaemic optic neuropathy (NAION) during treatment with semaglutide. There is no identified time interval for when NAION may develop following treatment start. A sudden loss of vision should lead to ophthalmological examination and treatment with semaglutide should be discontinued if NAION is confirmed (see section 4.8).

Patients with gastroparesis

Semaglutide treated patients with gastroparesis may experience more serious or severe gastrointestinal adverse events. Semaglutide should be used with caution in these patients, and semaglutide is not recommended if gastroparesis is severe (see section 4.8).

Populations not studied

The safety and efficacy of Kayshild have not been investigated in patients:
– with type 1 diabetes,
– with severe renal impairment (see section 4.2),
– with moderate or severe hepatic impairment and MASH (see section 4.2),
– with congestive heart failure New York Heart Association (NYHA) class IV.
Use in these patients is not recommended.

There is limited experience with Kayshild in patients:
– aged 75 years or more (see section 4.2),
– with moderate or severe hepatic impairment (see section 4.2),
– with inflammatory bowel disease,
– MASH and BMI< 25 kg/m^2 (or BMI< 23 kg/m^2 for Asian population).
Use with caution in these patients.

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

Semaglutide delays gastric emptying and could potentially influence the absorption of concomitantly administered oral medicinal products. However, no clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg, probably due to a tolerance effect. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption.

Warfarin and other coumarin derivatives

Semaglutide did not change 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. Upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of INR is recommended.

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. It 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

Women of childbearing potential

Women of childbearing potential are recommended to use contraception when treated with semaglutide (see section 4.5).

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3). There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2).

Breast-feeding

In lactating rats, semaglutide was excreted in milk. A risk to a breast-fed child cannot be excluded. Semaglutide should not be used during breast-feeding.

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

Semaglutide has no or negligible influence on the ability to drive and use machines. However, dizziness can be experienced mainly during the dose escalation period (see section 4.8). Driving or use of machines should be done cautiously if dizziness occurs.

Patients with type 2 diabetes

If semaglutide is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions during treatment with semaglutide in the phase 3 clinical trial in MASH (ESSENCE, see section 5.1) were gastrointestinal disorders including nausea (36.1%), diarrhoea (26.8%), constipation (22.1%), and vomiting (18.5%), and fatigue (see section ‘Description of selected adverse reactions’).

Tabulated list of adverse reactions

Table 2 lists adverse reactions identified with semaglutide. The frequencies presented are the highest if difference is observed in reporting between the phase 3 clinical trial in MASH (ESSENCE, see section 5.1), weight management phase 3a trials (STEP 1-4) and post-marketing reports.

Adverse reactions are listed by MedDRA system organ class and frequency. Frequency categories are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Adverse reactions

MedDRA system organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Immune system disorders				Anaphylactic reaction		
Metabolism and nutrition disorders		Hypoglycaemia in patients with type 2 diabetes[a]				
Nervous system disorders	Headache[a,b]	Dizziness[b] Dysaesthesia[a,c] Dysgeusia[b,c]				
Eye disorders		Diabetic retinopathy in patients with type 2 diabetes[a]			Non-arteritic anterior ischemic optic neuropathy (NAION)[a,d]	
Cardiac disorders		Hypotension	Orthostatic hypotension Increased heart rate[a,c]			
Gastrointestinal disorders	Vomiting[a,b] Diarrhoea[a,b] Constipation[a,b] Nausea[a,b] Abdominal pain[b,c]	Gastritis[b,c] Gastroesophageal reflux disease[b] Dyspepsia[b] Eructation[b] Flatulence[b] Abdominal distension[b] Delayed gastric emptying Gastroenteritis Increased lipase[c]	Acute pancreatitis[a] Increased amylase[c]			Intestinal obstruction[c,d,e]
Hepatobiliary disorders		Cholelithiasis[a]				
Skin and subcutaneous disorders		Hair loss[a]		Angioedema		
General disorders and administration site conditions	Fatigue[b,c]	Injection site reactions[c]				

a) See description of selected adverse reactions below
b) Mainly seen in the dose-escalation period
c) Grouped preferred terms
d) From post-marketing reports with other marketed semaglutide products
e) Grouped term covering PTs Intestinal obstruction, ileus, small intestinal obstruction

Description of selected adverse reactions

Gastrointestinal adverse reactions
The events were most frequently reported during dose escalation. In ESSENCE, nausea occurred in 36.1% of patients when treated with semaglutide (12.4% for placebo), diarrhoea in 26.8% (12.2% for placebo) and vomiting in 18.5% (5.6% for placebo). Most events were mild to moderate in severity and of short duration. Constipation occurred in 22.1% of patients treated with semaglutide (7.8% for placebo) and was mild to moderate in severity and of longer duration.
In ESSENCE, the gastrointestinal events led to permanent treatment discontinuation in 1.6% of patients treated with semaglutide.
In the weight management phase 3a trials with semaglutide 2.4 mg, over the 68 weeks trial period, nausea occurred in 43.9% of patients when treated with semaglutide (16.1% for placebo), diarrhoea in 29.7% (15.9% for placebo) and vomiting in 24.5% (6.3% for placebo). Most events were mild to moderate in severity and of short duration. Constipation occurred in 24.2% of patients treated with semaglutide (11.1% for placebo) and was mild to moderate in severity and of longer duration. In patients treated with semaglutide, median duration of nausea was 8 days, vomiting 2 days, diarrhoea 3 days, and constipation 47 days.

According to data from the weight management phase 3a trials with semaglutide 2.4 mg, patients with moderate renal impairment (eGFR $\geq$ 30 to < 60 mL/min/1.73m^2) may experience more gastrointestinal effects when treated with semaglutide.

Patients with gastroparesis may experience more serious or severe gastrointestinal effects when treated with semaglutide.

Acute pancreatitis
The frequency of acute pancreatitis reported in ESSENCE was 0.4% for semaglutide and 0.5% for placebo.
The frequency of adjudication-confirmed acute pancreatitis reported in the weight management phase 3a clinical trials with semaglutide 2.4 mg was 0.2% for semaglutide and < 0.1% for placebo, respectively. In SELECT, the cardiovascular outcomes trial, the frequency of acute pancreatitis confirmed by adjudication was 0.2% for semaglutide and 0.3% for placebo.

Acute gallstone disease/Cholelithiasis
In ESSENCE, cholelithiasis was reported in 1.4% of patients treated with semaglutide and in 0.8% of patients treated with placebo.
In the weight management phase 3a trials with semaglutide 2.4 mg, cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of patients treated with semaglutide. Cholelithiasis and cholecystitis was reported in 1.1% and 0.3%, respectively, of patients treated with placebo.

Headache
In ESSENCE, headache was reported in 8% of patients with semaglutide and in 6.3% of patients treated with placebo.
In the weight management phase 3a trials with semaglutide 2.4 mg, headache was reported in 12.8% of patients treated with semaglutide and in 8.7% of patients treated with placebo.

Hair loss
In ESSENCE, hair loss was reported in 1.6% of patients treated with semaglutide and in 0.5% of patients treated with placebo.
In the weight management phase 3a trials with semaglutide 2.4 mg, hair loss was reported in 2.5% of patients treated with semaglutide and in 1% of patients treated with placebo. The events were mainly of mild severity and most patients recovered while on continued treatment. Hair loss was reported more frequently in patients with a greater weight loss ($\geq$ 20%).

Increased heart rate
In ESSENCE, a mean increase of 2 beats per minute (bpm) at week 72 from a baseline mean of 75 bpm was observed in patients treated with semaglutide. The proportions of patients with a maximum increase from baseline ≥ 10 bpm at any timepoint during the on-treatment period were 43.3% in the semaglutide 2.4 mg group vs 50.4% in the placebo group.
In the weight management phase 3a trials with semaglutide 2.4 mg, a mean increase of 3 bpm from a baseline mean of 72 bpm was observed in patients treated with semaglutide. The proportions of subjects with an increase in pulse from baseline ≥ 10 bpm at any timepoint during the on-treatment period were 67% in the semaglutide group vs. 50.1% in the placebo group.

Immunogenicity
Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop antibodies following treatment with semaglutide. In ESSENCE, the proportion of patients testing positive for anti-semaglutide antibodies at any time post-baseline was low (0.4%).
In the weight management phase 3a trials with semaglutide 2.4 mg, the proportion of patients testing positive for anti-semaglutide antibodies at any time post-baseline was low (2.9%) and no patients had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect at end-of-trial. During treatment, high semaglutide concentrations might have lowered the sensitivity of the assays, hence the risk of false negatives cannot be excluded. However, in subjects testing positive for antibodies during and after treatment, the presence of antibodies was transient and with no apparent impact on efficacy and safety.

Dysaesthesia
In ESSENCE, events related to a clinical picture of altered skin sensation such as paraesthesia, hyperaesthesia, pain of skin, sensitive skin, dysaesthesia and burning skin sensation were reported in 2.9% of patients treated with semaglutide and 1.5% of patients treated with placebo.
In the weight management phase 3a trials with semaglutide 2.4 mg, events related to a clinical picture of altered skin sensation were reported in 2.1% of patients treated with semaglutide 2.4 mg and 1.2% of patients treated with placebo.
In both clinical development programmes, the events were mild to moderate in severity and most patients recovered while on continued treatment.

Hypoglycaemia in patients with type 2 diabetes
In ESSENCE, clinically significant hypoglycaemia (< 3.0 mmol/L) was observed in 6.1% (0.068 events/patient year) of patients treated with semaglutide compared with 5% (0.12 events/patient year) of patients treated with placebo. Severe hypoglycaemia (requiring external assistance for recovery) was reported with semaglutide in 2.2% of patients (0.015 events/patient year) and with placebo in 0.5% of patients (0.003 events/patient year).
In a phase 3a trial in adults with overweight or obesity and type 2 diabetes (STEP 2), clinically significant hypoglycaemia was observed in 6.2% (0.1 events/patient year) of subjects treated with semaglutide compared with 2.5% (0.03 events/patient year) of subjects treated with placebo. Hypoglycaemia with semaglutide was seen both with and without concomitant use of sulfonylurea. One episode (0.2% of subjects, 0.002 events/patient year) was reported as severe in a subject not concomitantly treated with a sulfonylurea. The risk of hypoglycaemia was increased when semaglutide was used with a sulfonylurea.

Diabetic retinopathy in patients with type 2 diabetes
A 2-year clinical trial investigated semaglutide 0.5 mg and 1 mg vs. placebo in 3 297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with semaglutide (3%) 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 trial.
In ESSENCE, retinal disorders were reported by 3.1% of patients treated with semaglutide and 4.1% of patients treated with placebo. Few patients reported diabetic retinopathy (1.1%, and 1.4%, respectively).

In a phase 3a trial in adults with overweight or obesity and type 2 diabetes (STEP 2), retinal disorders were reported by 6.9% of patients treated with semaglutide 2.4 mg, 6.2% of patients treated with semaglutide 1 mg, and 4.2% of patients treated with placebo. The majority of events were reported as diabetic retinopathy (4%, 2.7%, and 2.7%, respectively) and non-proliferative retinopathy (0.7%, 0%, and 0%, respectively).

Non-arteritic anterior ischaemic optic neuropathy (NAION)
Results from several large epidemiological studies suggest that exposure to semaglutide in adults with type 2 diabetes is associated with an approximately two-fold increase in the relative risk of developing NAION, corresponding to approximately one additional case per 10 000 person-years of treatment.

Paediatric population

Semaglutide has not been studied in children and adolescents below 18 years with MASH.

In a clinical trial conducted in adolescents of 12 years to below 18 years with obesity or overweight with at least one weight-related comorbidity, 133 patients were exposed to semaglutide. The trial duration was 68 weeks.
Overall, the frequency, type and severity of adverse reactions in the adolescents were comparable to that observed in the adult population. Cholelithiasis was reported in 3.8% of patients treated with semaglutide and 0% of patients treated with placebo.
No effects on growth or pubertal development were found after 68 weeks of treatment.

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

Overdose with semaglutide may be associated with gastrointestinal disorders which could lead to dehydration. In the event of overdose, the patient should be observed for clinical signs and appropriate supportive treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, glucagon-like peptide-1 (GLP-1) analogues, ATC code: A10BJ06

Mechanism of action

Semaglutide is a GLP-1 analogue with 94% sequence homology 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 receptors are widely distributed throughout the body (e.g. pancreas, kidney, brain, heart, vasculature, immune system and lung); however, they have not been detected on liver cells.

The liver-specific mechanism of action is multifactorial and thought to be mediated through improvement in metabolic factors, including weight loss, improved glucose and lipid metabolism, and reduced inflammation. Semaglutide affects gene pathways of both inflammation and fibrosis, consequently positively changing the proteomic pattern of an individual with MASH. Moreover, semaglutide lowers liver fat deposition.

Semaglutide lowers body weight through reduced appetite and thereby reduced energy intake. In addition, semaglutide reduces the preference for high-fat foods.

Furthermore, semaglutide reduces blood glucose levels in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose levels are 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 has a beneficial effect on blood lipid levels and results in lower systolic blood pressure and reduced inflammation. Furthermore, animal studies have shown that semaglutide attenuates the development of atherosclerosis and has an anti-inflammatory action in the cardiovascular system.

Pharmacodynamic effects

MASH disease activity
Semaglutide improves components of the MASH disease activity by reducing steatosis, inflammation and ballooning assessed by histology. Additionally, semaglutide reduces liver steatosis assessed by transient elastography (TE) using Controlled Attenuation Parameter (CAP) and Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF).
Improvements in the levels of alanine transaminase (ALT) and aspartate aminotransferase (AST) have also been observed.

Liver fibrosis
Semaglutide decreases liver stiffness assessed by TE and reduces the Enhanced Liver Fibrosis (ELF) score and the levels of the pro-peptide of type III collagen biomarker (Pro-C3).

Fasting lipids
Semaglutide compared to placebo lowered fasting triglyceride concentration by 17% and improved HDL concentration by 4.7%.

Glucose and insulin sensitivity
In patients with MASH and type 2 diabetes, semaglutide reduced HbA1c by 1.1% compared with placebo (0%).
In patients with MASH without type 2 diabetes, the estimated reduction in homeostasis model assessment of insulin resistance (HOMA-IR) was greater with semaglutide (-32.5%) than with placebo (-0.5%).

Glucose-dependent insulin and glucagon secretion
Semaglutide lowers high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose-dependent manner. With semaglutide, the insulin secretion rate in patients with type 2 diabetes was comparable to that of healthy subjects.
During induced hypoglycaemia, semaglutide compared with placebo did not alter the counter regulatory responses of increased glucagon and did not impair the decrease of C-peptide in patients with type 2 diabetes.

Clinical efficacy and safety

The efficacy and safety of semaglutide have been evaluated in one phase 3 trial (ESSENCE) in adult patients with MASH and F2 or F3.

ESSENCE is a 240-week, randomised, multicentre, double-blind, parallel-group trial. Enrolled patients had a baseline or recent liver biopsy showing clinically significant metabolic dysfunction-associated steatotic liver disease (MASLD), defined as MASH with F2 or F3 and non-alcoholic fatty liver disease activity score (NAS) ≥ 4 with a score of 1 or more in steatosis, lobular inflammation and hepatocyte ballooning. Efficacy determination was based on the effect of semaglutide on resolution of

steatohepatitis (defined as a NAS of 0–1 for inflammation, 0 for ballooning, and any value for steatosis (According to NASH CRN)) with no worsening of liver fibrosis (fibrosis is graded on the NASH CRN fibrosis scale from 0 to 4) and on at least one stage improvement in liver fibrosis (defined as ≥ 1 grade improvement on the NASH CRN fibrosis scale) with no worsening of steatohepatitis (defined as no increase from baseline in NAS score for ballooning, inflammation, or steatosis), on post-baseline liver biopsies collected at 72 weeks.
A total of 800 patients randomised to semaglutide (534 patients) or placebo (266 patients) in a 2 to 1 ratio were included in the interim analysis at week 72. Of these, 31.3% had MASH and F2 and 68.8% had MASH and F3 as assessed at baseline. The mean age was 56 years and 25.3% were above 65 years. 57.1% were female. The mean BMI was 34.6 kg/m^2, 6.6% had BMI< 25, 72.8% had BMI≥ 30 and 55.9% had type 2 diabetes. The baseline value for liver stiffness assessed by TE (geom. mean) was 11.5 kPa, for ELF score (median) 9.9, for FIB-4 (median) 1.6, for ALT (geom. mean) 56.8 units/L and for AST (geom. mean) 46.6 units/L.

At week 72, semaglutide was superior to placebo in inducing resolution of steatohepatitis with no worsening of liver fibrosis, in inducing improvement in liver fibrosis with no worsening of steatohepatitis, as well as resolution of steatohepatitis with improvement in liver fibrosis (see Table 3). Treatment with semaglutide also resulted in a greater and sustained weight loss and improvements in non-invasive liver-related tests compared with placebo at week 72 (see Table 3).

Efficacy was observed regardless of age, gender, race and ethnicity, as well as baseline fibrosis stage, hepatic function, BMI, presence of type 2 diabetes and level of renal function.

Table 3 ESSENCE: Results at week 72

	semaglutide 2.4 mg	**placebo**
Full analysis set (N)	534	266
Resolution of steatohepatitis and no worsening of liver fibrosis[1]		
Proportion (%) of responders[2]	62.9	34.3
Difference (%-point) from placebo[3] [95% CI]	28.6 [21.1; 36.2]*	-
Improvement in liver fibrosis and no worsening of steatohepatitis[4]		
Proportion (%) of responders[2]	36.8	22.4
Difference (%-point) from placebo[3] [95% CI]	14.4 [7.5; 21.3]*	-
Resolution of steatohepatitis and improvement in liver fibrosis[5]		
Proportion (%) of responders[2]	32.7	16.1
Difference (%-point) from placebo[3] [95% CI]	16.5 [10.2; 22.8]*	-
Body weight		
Baseline (kg)	95.4	97.6
Change (%) from baseline[6]	-10.5	-2.0
Difference (%-point) from placebo[6] [95% CI]	-8.5 [-9.5; -7.4]*	-
Liver stiffness assessed by TE		
Number of patients at baseline[7]	417	216
Baseline (kPa)[8]	11.5	11.6
Change (%) from baseline[6]	-31.1	-13.5
Relative difference (%) from placebo[6] [95% CI]	-20.4 [-25.9; -14.4]	-
ELF score		
Baseline	10.0	10.0
Change from baseline[6]	-0.57	0.01
Difference from placebo[6] [95% CI]	-0.57 [-0.68; -0.47]	-
ALT		
Baseline (units/L)[8]	57.1	56.4
Change (%) from baseline[6]	-52.1	-22.2
Relative difference (%) from placebo[6] [95% CI]	-38.5 [-43.4; -33.1]	-
AST		
Baseline (units/L)[8]	46.9	45.9
Change (%) from baseline[6]	-44.9	-17.1
Relative difference (%) from placebo[6] [95% CI]	-33.5 [-37.9; -28.9]	-

ALT: alanine transaminase, AST: aspartate aminotransferase, ELF: enhanced liver fibrosis, TE: transient elastography
* p< 0.0001 (unadjusted 2-sided) for superiority.
[1]Resolution of steatohepatitis is defined as a non-alcoholic fatty liver disease (NAFLD) Activity Score (NAS) of 0–1 for inflammation, 0 for ballooning, and any value for steatosis (According to non-alcoholic steatohepatitis Clinical Research Network (NASH CRN)). Fibrosis is graded on the NASH CRN fibrosis scale from 0 to 4.
[2]Missing observations were imputed with multiple imputation (MI) based on unconditional reference.
[3] Estimated with a Cochran-Mantel-Haenszel test stratified by baseline diabetes status and baseline fibrosis status.
[4]Improvement in fibrosis is defined as ≥ 1 grade improvement on the NASH CRN fibrosis scale. No worsening of steatohepatitis is defined as no increase from baseline in NAS score for ballooning, inflammation, or steatosis.
[5]Resolution of steatohepatitis is defined as an NAS of 0–1 for inflammation, 0 for ballooning, and any value for steatosis (According to NASH CRN). Improvement in fibrosis is defined as ≥ 1 grade improvement on the NASH CRN fibrosis scale.
[6]Estimated using an ANCOVA model using multiple imputation based on unconditional reference.
[7] Patients from sites with available equipment
[8] Geometric mean

Cardiovascular safety
As based on the findings of the randomised, double-blind, placebo-controlled, event driven SELECT trial which included 17 604 patients with established cardiovascular disease and BMI≥27 kg/m^2,there is no sign of any detrimental cardiovascular safety issue with a hazard ratio (HR) of 0.80, [0.72; 0.90] [95% CI]), for major adverse cardiovascular events (MACE), defined as a composite endpoint consisting of cardiovascular death (including undetermined cause of death), non-fatal myocardial infarction, or non-fatal stroke. Each component contributed to the reduction of MACE.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Kayshild in one or more subsets of the paediatric population in the treatment of MASH (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week making it suitable for once-weekly subcutaneous administration. The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilised against degradation by the DPP-4 enzyme.

Absorption

The average semaglutide steady state concentration following subcutaneous administration of the semaglutide maintenance dose was approximately 80 nmol/L in patients with MASH and F2 or F3 based on data from a phase 3a trial, where 90% of patients had average concentrations between 52 nmol/L and 122 nmol/L. The steady state exposure of semaglutide increased proportionally with doses from 0.25 mg up to 2.4 mg once weekly. Steady state exposure was stable with time as assessed up to week 72. Similar exposure was achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm. The absolute bioavailability of semaglutide was 89%.

Distribution

The mean volume of distribution of semaglutide following subcutaneous administration in patients with MASH and F2 or F3 was approximately 13.7 L. Semaglutide was extensively bound to plasma albumin (> 99%).

Biotransformation

Prior to excretion, semaglutide is extensively metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain. The enzyme neutral endopeptidase (NEP) was identified as one of the active metabolic enzymes.

Elimination

The primary excretion routes of semaglutide-related material are via the urine and faeces. Approximately 3% of the absorbed dose was excreted in the urine as intact semaglutide.
The clearance of semaglutide in patients with MASH and F2 or F3 was approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for approximately 7 weeks after the last dose of 2.4 mg.

Special populations

Elderly
Age had no effect on the pharmacokinetics of semaglutide based on data from phase 2 and phase 3 trials including patients 18–80 years of age.

Gender, race and ethnicity
Gender (494 female, 326 male), race (White and other (641 patients), Asian (179 patients)) and ethnicity (Hispanic or Latino (137 patients), non-Hispanic or -Latino (683 patients)) had no effect on the pharmacokinetics of semaglutide based on data from phase 2 and phase 3 trials.

Body weight
Body weight had an effect on the exposure of semaglutide. Higher body weight was associated with lower exposure; a 20% difference in body weight between individuals will result in an approximate 19% difference in exposure. The 2.4 mg weekly dose of semaglutide provided adequate systemic exposures over the body weight range of 42.7−206 kg.

Renal impairment
Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown with a single dose of 0.5 mg semaglutide for patients with different degrees of renal impairment (mild, moderate, severe or patients in dialysis) compared with patients with normal renal function. This was also shown for patients with MASH and mild to moderate renal impairment based on data from phase 2 and phase 3 trials.

Hepatic impairment
Hepatic impairment did not have any impact on the exposure of semaglutide. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic impairment (mild (Child-Pugh A), moderate (Child-Pugh B), severe (Child-Pugh C)) and compared with patients with normal hepatic function in a study with a single dose of 0.5 mg semaglutide.

Liver fibrosis
The stage of liver fibrosis (F1 to F4c) did not have any effect on the exposure of semaglutide based on data from phase 2 and phase 3 trials.

Diabetes status
Type 2 diabetes did not have any impact on the exposure of semaglutide based on data from phase 2 and phase 3 trials.

Immunogenicity
Development of anti-semaglutide antibodies when treated with semaglutide occurred infrequently (see section 4.8) and the response did not appear to influence semaglutide pharmacokinetics.

Paediatric population
Safety and efficacy of semaglutide in children and adolescents with MASH below 18 years of age have not been studied.
Pharmacokinetic properties for semaglutide were assessed in a clinical trial for adolescent patients with obesity or overweight and at least one weight-related comorbidity ages 12 to < 18 years (124 patients, body weight 61.6-211.9 kg). The semaglutide exposure in adolescents was similar to that in adults with obesity or overweight.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional 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

Disodium phosphate, dihydrate
Propylene glycol
Phenol
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before use: 3 years.
After first use: 6 weeks. Store below 30 °C or in a refrigerator (2 °C to 8 °C).

6.4 Special precautions for storage

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

Keep the pen cap on when the pen is not in use in order to protect it from light.

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

6.5 Nature and contents of container

1.5 mL or 3 mL glass cartridge (type I glass) closed at the one end with a rubber plunger (chlorobutyl) and at the other end with an aluminium cap with a laminated rubber sheet (bromobutyl/polyisoprene) inserted. The cartridge is assembled into a disposable pre-filled pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

Pack size of 1 pre-filled pen and 4 disposable NovoFine Plus needles.

6.6 Special precautions for disposal and other handling

Kayshild should not be used if it does not appear clear and colourless.
The pen should not be used if it has been frozen.

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

The pen is for multi-use. It contains four (4) doses. After having injected the 4 doses, there might still be solution left in the pen despite having administered correctly. Any solution left is insufficient for a dose and the pen should be disposed of.

The patient should be advised to discard the injection needle in accordance with local requirements after each injection and store the Kayshild pen without an injection needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

The pen is for use by one person only.

Kayshild can be administered with 30G, 31G and 32G disposable needles up to a length of 8 mm.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/26/2019/001
EU/1/26/2019/002
EU/1/26/2019/003
EU/1/26/2019/004
EU/1/26/2019/005

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.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS 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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

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

Name and address of the manufacturer of the biological active substance

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

Name and address of the manufacturers responsible for batch release

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

Novo Nordisk Production SAS
45, Avenue d'Orléans
28000 Chartres
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

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.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Post-authorisation efficacy study (PAES): NN9931-4553 (ESSENCE) In order to confirm the efficacy and safety of semaglutide in adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3), the MAH shall submit the final results of NN9931-4553 (ESSENCE), a phase III, double-blind, randomized, placebo-controlled study.	31 Dec 2029

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kayshild 0.25 mg solution for injection in pre-filled pen
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 1 mg semaglutide in 1.5 mL (0.68 mg/mL)

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid/sodium hydroxide (for pH adjustment), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
FlexTouch
1 pen and 4 disposable needles (1 pen = 4 doses)

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
once weekly

Read the package leaflet before use.

Use Kayshild once a week

Write the weekday you choose to inject

I injected my weekly dose on the below dates

Open here

Lift 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

Do not store the pen with a needle attached.
For use by one person only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
After the first use of the pen, store below 30 °C or in a refrigerator. Do not freeze.
Keep the pen cap on in order to protect from light.
Discard pen 6 weeks after first use.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER

EU/1/26/2019/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kayshild 0.25 mg

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

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Kayshild 0.25 mg injection
FlexTouch
semaglutide
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

1.5 mL
(4 doses)

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kayshild 0.5 mg solution for injection in pre-filled pen
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 2 mg semaglutide in 3 mL (0.68 mg/mL)

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid/sodium hydroxide (for pH adjustment), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
FlexTouch
1 pen and 4 disposable needles (1 pen = 4 doses)

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
once weekly

Read the package leaflet before use.

Use Kayshild once a week

Write the weekday you choose to inject

I injected my weekly dose on the below dates

Open here

Lift 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

Do not store the pen with a needle attached.
For use by one person only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
After the first use of the pen, store below 30 °C or in a refrigerator. Do not freeze.
Keep the pen cap on in order to protect from light.
Discard pen 6 weeks after first use.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER

EU/1/26/2019/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kayshild 0.5 mg

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

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Kayshild 0.5 mg injection
FlexTouch
semaglutide
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

3 mL
(4 doses)

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kayshild 1 mg solution for injection in pre-filled pen
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 4 mg semaglutide in 3 mL (1.34 mg/mL)

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid/sodium hydroxide (for pH adjustment), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
FlexTouch
1 pen and 4 disposable needles (1 pen = 4 doses)

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
once weekly

Read the package leaflet before use.

Use Kayshild once a week

Write the weekday you choose to inject

I injected my weekly dose on the below dates

Open here

Lift 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

Do not store the pen with a needle attached.
For use by one person only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
After the first use of the pen, store below 30 °C or in a refrigerator. Do not freeze.
Keep the pen cap on in order to protect from light.
Discard pen 6 weeks after first use.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER

EU/1/26/2019/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kayshild 1 mg

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

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Kayshild 1 mg injection
FlexTouch
semaglutide
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

3 mL
(4 doses)

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kayshild 1.7 mg solution for injection in pre-filled pen
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 6.8 mg semaglutide in 3 mL (2.27 mg/mL)

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid/sodium hydroxide (for pH adjustment), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
FlexTouch
1 pen and 4 disposable needles (1 pen = 4 doses)

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
once weekly

Read the package leaflet before use.

Use Kayshild once a week

Write the weekday you choose to inject

I injected my weekly dose on the below dates

Open here

Lift 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

Do not store the pen with a needle attached.
For use by one person only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
After the first use of the pen, store below 30 °C or in a refrigerator. Do not freeze.
Keep the pen cap on in order to protect from light.
Discard pen 6 weeks after first use.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER

EU/1/26/2019/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kayshild 1.7 mg

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

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Kayshild 1.7 mg injection
FlexTouch
semaglutide
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

3 mL
(4 doses)

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kayshild 2.4 mg solution for injection in pre-filled pen
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 9.6 mg semaglutide in 3 mL (3.2 mg/mL)

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid/sodium hydroxide (for pH adjustment), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
FlexTouch
1 pen and 4 disposable needles (1 pen = 4 doses)

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
once weekly

Read the package leaflet before use.

Use Kayshild once a week

Write the weekday you choose to inject

I injected my weekly dose on the below dates

Open here

Lift 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

Do not store the pen with a needle attached.
For use by one person only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
After the first use of the pen, store below 30 °C or in a refrigerator. Do not freeze.
Keep the pen cap on in order to protect from light.
Discard pen 6 weeks after first use.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/26/2019/005

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kayshild 2.4 mg

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

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Kayshild 2.4 mg injection
FlexTouch
semaglutide
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

3 mL
(4 doses)

6. OTHER

Novo Nordisk A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kayshild 0.25 mg solution for injection in pre-filled pen
Kayshild 0.5 mg solution for injection in pre-filled pen
Kayshild 1 mg solution for injection in pre-filled pen
Kayshild 1.7 mg solution for injection in pre-filled pen
Kayshild 2.4 mg solution for injection in pre-filled pen
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 Kayshild is and what it is used for

Kayshild is a medicine that contains the active substance semaglutide. It is used in combination with diet and exercise to treat adults with metabolic dysfunction-associated steatohepatitis (MASH). It is used in adults who have moderate to advanced liver fibrosis (scarring) without cirrhosis (severe, irreversible scarring). MASH is a condition where fat builds up in the liver, which can result in inflammation, liver damage and development of scar tissue.

The active substance in Kayshild, semaglutide, is similar to a natural hormone called glucagon-like peptide-1 (GLP-1). In the liver it reduces liver damage, likely due to improvements in metabolic factors, such as weight loss, improved blood sugar and lipid levels and lessening of inflammation.

2. What you need to know before you use Kayshild

Do not use Kayshild
- if you are allergic to 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 Kayshild.

The use of Kayshild is not recommended if you:
- have type 1 diabetes,
- have severely reduced kidney function,
- have moderately or severely reduced liver function and MASH,
- have severe heart failure,
- have diabetic eye disease (retinopathy).

There is little experience with Kayshild in patients:
- of 75 years and older,
- with moderately or severely reduced liver function,
- with inflammatory bowel disease,
- with MASH and a body mass index (BMI) of less than 25 kg/m^2 (or a BMI less than 23 kg/m^2 for Asian people).

Please consult your doctor if one of the above applies to you.

If you know that you are due to have surgery where you will be under anaesthesia (sleeping), please tell your doctor that you are taking Kayshild.

- **Dehydration**
  During treatment with Kayshild, you may feel sick (nausea) or be sick (vomiting), or have diarrhoea. These side effects can cause dehydration (loss of fluids). It is important that you drink enough fluids to prevent dehydration. This is especially important if you have kidney problems. Talk to your doctor if you have any questions or concerns.

- **Inflammation of the pancreas**
  If you have severe and ongoing pain in the stomach area (see section 4) – see a doctor straight away as this could be a sign of inflamed pancreas (acute pancreatitis).

- **People with type 2 diabetes**
  Kayshild cannot be used as a substitute for insulin. Do not use Kayshild in combination with other medicines that contain GLP-1 receptor agonists (such as liraglutide, dulaglutide, exenatide or lixisenatide).

- **Low blood sugar (hypoglycaemia)**
  Taking a sulfonylurea or an insulin with Kayshild might increase the risk of getting low blood sugar levels (hypoglycaemia). Please see section 4 for the warning signs of low blood sugar levels. Your doctor may ask you to test your blood sugar levels. This will help your doctor decide if the dose of the sulfonylurea or insulin needs to be changed to reduce the risk of low blood sugar.

- **Diabetic eye disease (retinopathy)**
  If you have diabetic eye disease and are using insulin, this medicine may lead to a worsening of your vision, and this may require treatment. Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disease. If you have diabetic eye disease and experience eye problems while taking this medicine, talk to your doctor.

- **Sudden changes to your eyesight**
  If you notice a sudden loss of vision or rapidly worsening eyesight during treatment with this medicine, immediately contact your doctor for advice. This may be caused by a very rare side effect called non-arteritic anterior ischaemic optic neuropathy (NAION) (see section 4: 'Serious side effects'). Your doctor may refer you for an eye examination and you may have to stop treatment with this medicine.

- **Patients with delayed stomach emptying (gastroparesis)**
  If you have slow (delayed) stomach emptying (called gastroparesis), use of Kayshild may lead to serious or severe gastrointestinal adverse events. Talk to your doctor before using Kayshild.

Children and adolescents
The safety and efficacy of Kayshild in children and adolescents below 18 years of age have not been studied and Kayshild is not recommended for use in this population.

Other medicines and Kayshild
Tell your doctor, pharmacist or nurse if you are using, have recently used or might use any other medicines.

In particular, tell your doctor, pharmacist or nurse if you are using medicines containing the following:
- Warfarin or other similar medicines taken by mouth to reduce blood clotting (oral anti-coagulants). When you start treatment with e.g. warfarin or similar medicines, frequent blood testing to determine the ability of your blood to clot may be required.

Pregnancy and breast-feeding
This medicine should not be used during pregnancy, as it is not known if it may affect your unborn child. Therefore, it is recommended to use contraception while using this medicine. If you wish to become pregnant, you should stop using this medicine at least two months in advance. If you become or are pregnant, think you may be pregnant or are planning to have a baby when using this medicine, talk to your doctor straight away, as your treatment will need to be stopped.

Do not use this medicine if you are breast-feeding, as it is unknown if it passes into breast milk.

Driving and using machines
Kayshild is unlikely to affect your ability to drive and use machines. Some patients may feel dizzy when taking Kayshild mainly during the first 4 months of treatment (see section 4). If you feel dizzy, be extra careful while driving or using machines. If you need any further information, talk to your doctor, pharmacist or nurse.

People with type 2 diabetes
If you use this medicine in combination with a sulfonylurea or insulin, low blood sugar (hypoglycaemia) may occur which may reduce your ability to concentrate. Avoid driving or using machines if you get any signs of low blood sugar. See section 2, 'Warnings and precautions' for information on increased risk of low blood sugar and section 4 for the warning signs of low blood sugar. Talk to your doctor for further information.

Kayshild 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 Kayshild

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

How much to use
The recommended dose is 2.4 mg once weekly.
Your treatment will start at a low dose, which will be gradually increased over 16 weeks of treatment.
- When you first start using Kayshild, the starting dose is 0.25 mg once weekly.
- Your doctor will instruct you to gradually increase your dose every 4 weeks until you reach the recommended dose of 2.4 mg once weekly.
- Once you reach the recommended dose of 2.4 mg, do not increase this dose further.
- In case you are feeling very bothered by sickness (nausea) or by being sick (vomiting) talk with your doctor about delaying dose escalation or lowering to the previous dose until symptoms have improved.

Usually, you will be told to follow the table below.

Dose escalation	Weekly dose
Week 1–4	0.25 mg
Week 5–8	0.5 mg
Week 9–12	1 mg
Week 13–16	1.7 mg
From week 17	2.4 mg

Your doctor will assess your treatment on a regular basis.

How Kayshild is given
Kayshild is given as an injection under the skin (subcutaneous injection). Do not inject it into a vein or muscle.
- The best places to give the injection are the front of your upper arm, upper legs or stomach.
- Before you use the pen for the first time, your doctor, pharmacist or nurse will show you how to use it.

Detailed instructions on how to use the pen are on the other side of this leaflet.

People with type 2 diabetes
Tell your doctor if you have type 2 diabetes. Your doctor may adjust the dose of your diabetes medicines to prevent you from getting low blood sugar.

When to use Kayshild
- You should use this medicine once a week and if possible, on the same day each week.
- You can give yourself the injection at any time of the day – regardless of meals.

If necessary, you can change the day of your weekly injection of this medicine as long as it has been at least 3 days since your last injection. After selecting a new dosing day, continue with once a week dosing.

If you use more Kayshild than you should
Talk to your doctor straight away. You may get side effects such as feeling sick (nausea), being sick (vomiting) or have diarrhoea, which may cause dehydration (loss of fluids).

If you forget to use Kayshild
If you forgot to inject a dose and:
- it is 5 days or less since you should have used Kayshild, use it as soon as you remember. Then inject your next dose as usual on your scheduled day.
- it is more than 5 days since you should have used Kayshild, skip the missed dose. Then inject your next dose as usual on your next scheduled day.

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

If you stop using Kayshild
Do not stop using this medicine without talking to your doctor.

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

Common (may affect up to 1 in 10 people)
- Complications of diabetic eye disease (diabetic retinopathy). If you have diabetes you should inform your doctor if you experience eye problems, such as changes in vision, during treatment with this medicine.

Uncommon (may affect up to 1 in 100 people)
- Inflamed pancreas (acute pancreatitis). Signs of inflamed pancreas may include severe and long-lasting pain in your stomach, the pain may move to your back. You should see your doctor immediately if you experience such symptoms.

Rare (may affect up to 1 in 1 000 people)
- Severe allergic reactions (anaphylactic reactions, angioedema). You should seek immediate medical help and inform your doctor straight away if you get symptoms such as breathing difficulty, swelling, light-headedness, fast heartbeat, sweating and loss of consciousness or rapid swelling under the skin in areas such as the face, throat, arms and legs, which can be life threatening if throat swelling blocks the airway.

Very rare (may affect up to 1 in 10 000 people)
- A medical condition of the eye called non-arteritic anterior ischaemic optic neuropathy (NAION), which may cause loss of vision to one of your eyes without any pain. You should immediately contact your doctor if you notice sudden or gradually worsening eyesight (see section 2: ‘Sudden changes to your eyesight’).

Not known (frequency cannot be estimated from the available data)
- Bowel obstruction. A severe form of constipation with additional symptoms such as stomach ache, bloating, vomiting etc.

Other side effects

Very common (may affect more than 1 in 10 people)
- headache
- feeling sick (nausea)
- being sick (vomiting)
- diarrhoea
- constipation
- stomach pain
- feeling weak or tired

– these are mainly seen during dose escalation and usually go away over time.

Common (may affect up to 1 in 10 people)
- feeling dizzy
- upset stomach or indigestion
- burping
- gas (flatulence)
- bloating of the stomach
- inflamed stomach ('gastritis') – the signs include stomach-ache, feeling sick (nausea) or being sick (vomiting)
- reflux or heartburn – also called 'gastro-oesophageal reflux disease'
- gallstones
- hair loss
- injection site reactions
- change in skin sensation
- a delay in the emptying of the stomach
- increase of pancreatic enzymes (such as lipase) shown in blood tests
- inflammation of the stomach and gut (gastroenteritis)
- low blood pressure
- change in the way food or drink tastes
- low blood sugar (hypoglycaemia) in patients with type 2 diabetes.

The warning signs of low blood sugar may come on suddenly. They can include: cold sweat, cool pale skin, headache, fast heartbeat, feeling sick (nausea) or very hungry, changes in vision, feeling sleepy or weak, feeling nervous, anxious or confused, difficulty concentrating or shaking.
Your doctor will tell you how to treat low blood sugar and what to do if you notice these warning signs.
Low blood sugar is more likely to happen if you also take a sulfonylurea or insulin. Your doctor may reduce your dose of these medicines before you start using this medicine.

Uncommon (may affect up to 1 in 100 people)
- fast heartbeat
- increase of pancreatic enzymes (such as amylase) shown in blood tests
- feeling dizzy or lightheaded on standing or sitting up because of a drop in blood pressure.

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 Kayshild

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 and carton after 'EXP'. The expiry date refers to the last day of that month.

Before opening
Store in a refrigerator (2 °C – 8 °C). Do not freeze. Keep away from the cooling element.

During use
- You can keep the pen for 6 weeks when stored at a temperature below 30 °C or in a refrigerator (2 °C – 8 °C) away from the cooling element. Do not freeze Kayshild and do not use it if it has been frozen.
- When you are not using the pen, keep the pen cap on in order to protect from light.

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

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 Kayshild contains

- The active substance is semaglutide.

  Kayshild 0.25 mg solution for injection
  Each pre-filled pen contains 1 mg semaglutide in 1.5 mL (0.68 mg/mL).

  Kayshild 0.5 mg solution for injection
  Each pre-filled pen contains 2 mg semaglutide in 3 mL (0.68 mg/mL).

  Kayshild 1 mg solution for injection
  Each pre-filled pen contains 4 mg semaglutide in 3 mL (1.34 mg/mL).

  Kayshild 1.7 mg solution for injection
  Each pre-filled pen contains 6.8 mg semaglutide in 3 mL (2.27 mg/mL).

  Kayshild 2.4 mg solution for injection
  Each pre-filled pen contains 9.6 mg of semaglutide in 3 mL (3.2 mg/mL).

- The other ingredients are disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid/sodium hydroxide (for pH adjustment), water for injections. See also section 2 ‘Kayshild contains sodium’ for information on sodium.

What Kayshild looks like and contents of the pack
Kayshild is a clear and colourless solution for injection in a pre-filled pen.

Each pre-filled pen contains four (4) doses. After having injected the 4 doses, there might still be solution left in the pen despite having administered correctly. Any solution left is insufficient for a dose and the pen should be disposed of.

Pack size: 1 pre-filled pen and 4 disposable NovoFine Plus needles.

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

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

Novo Nordisk Production SAS
45, Avenue d'Orléans
28000 Chartres
France

This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

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

Instructions on how to use Kayshild

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

Kayshild pen is a dial-a-dose pen that **contains four of your prescribed doses of Kayshild, corresponding to four times of once-weekly use.**

Please use the table inside the lid of the carton to keep track of how many injections you have taken and how many doses remain in your pen.

Kayshild comes in five different pen variants, each containing one of the following prescribed doses of semaglutide:

0.25 mg | **0.5 mg** | **1 mg** | **1.7 mg** | **2.4 mg**

Always start by checking your pen label to make sure that it contains your prescribed dose of Kayshild.

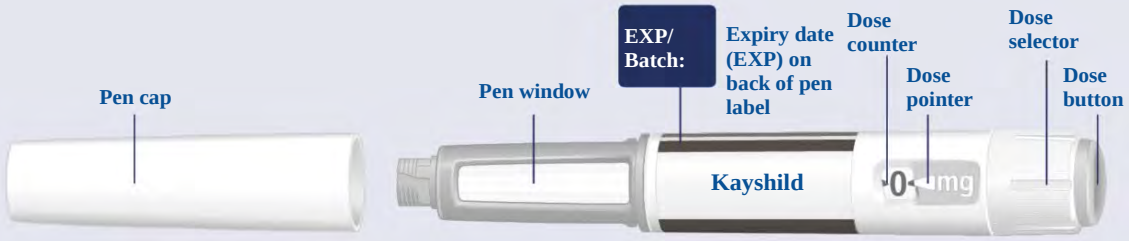
Your pen is designed to be used with 30G, 31G, and 32G disposable needles up to a length of 8 mm.

The pack contains:

- Kayshild pen
- 4 NovoFine Plus needles
- Package leaflet

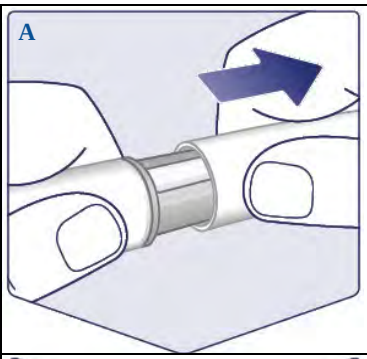
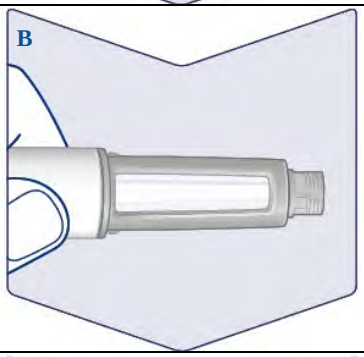
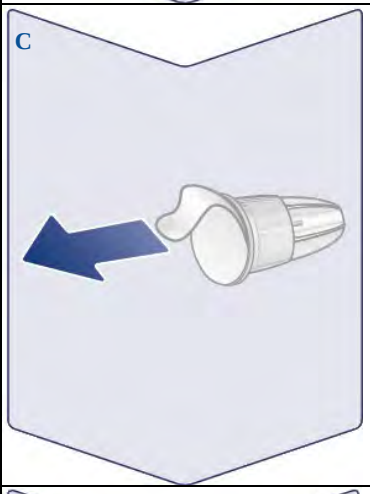
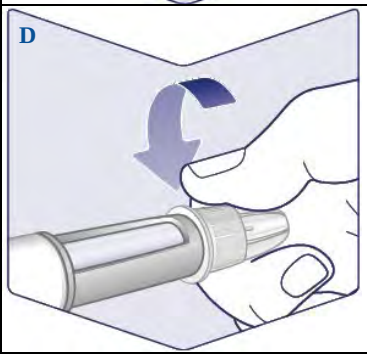
Kayshild pen (example)

Please note: Your pen may differ in size and your pen label may differ in colour from the example shown in the pictures.
These instructions apply to all Kayshild pens.



NovoFine Plus needle (example)

1. Prepare your pen with a new needle

Check the name and dose of your pen to make sure that it contains your prescribed dose of Kayshild. **Pull off the pen cap.** (See figure A).	
Check that the solution in your pen is clear and colourless. Look through the pen window. If Kayshild looks cloudy or coloured, do not use the pen. (See figure B).	
Always use a new needle for each injection. **Take a needle** when you are ready to take your injection. Check the paper tab and the outer needle cap for damages. If you see any damage, this could affect sterility. Dispose of it and use a new needle. **Tear off the paper tab.** (See figure C).	
Push the needle straight onto the pen. Turn until it is on tight. (See figure 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 Kayshild.

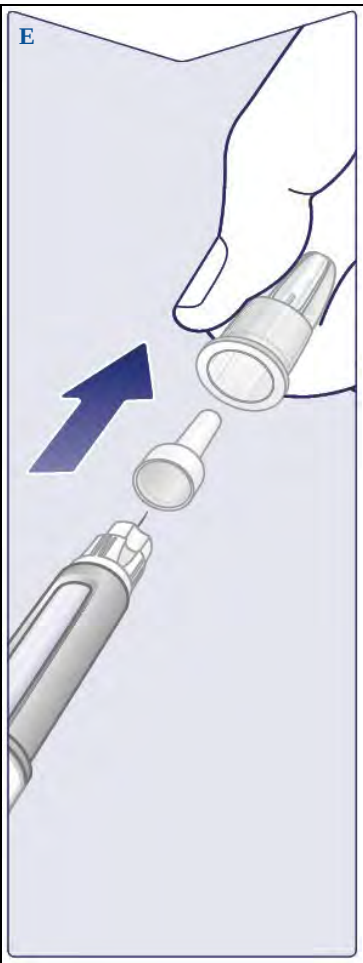
Pull off the outer needle cap and keep it for later. You will need it to safely remove the needle from the pen after the injection.

Pull off the inner needle cap and dispose of it. A drop of Kayshild may appear at the needle tip. You must still check the Kayshild flow if you use a new pen for the first time. See **'Check the flow with each new pen'.**

Never use a bent or damaged needle. For more information about needle handling, see **'About your needles'** below these instructions.

(See figure E).

E



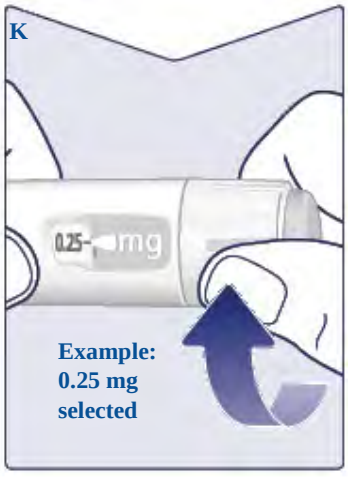
Check the flow with each new pen

If your Kayshild pen is already in use, go to **'2 Set your dose'.**
Only check the Kayshild flow before your **first injection with each new pen.**
Turn the dose selector until you see the flow check symbol (▪ ▪ ▬).

(See figure F).

F

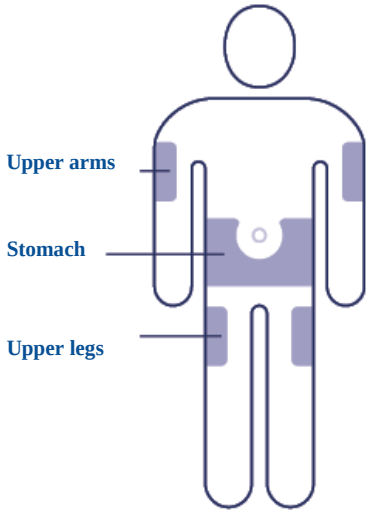
Make sure that the flow check symbol lines up with the dose pointer. (See figure G).	G 
Check the flow	
Hold the pen with the needle pointing up. **Press and hold in the dose button** until the dose counter returns to -0-. The -0- must line up with the dose pointer. A drop of Kayshild should appear at the needle tip. This drop indicates that your pen is ready for use. If a drop does not appear, check the flow again. **This should only be done twice.** If there is still no drop, **change the needle and check the flow once more.** **Do not use the pen** if a drop of Kayshild still does not appear. (See figure H).	H 
2. Set your dose	

Turn the dose selector until the **dose counter stops,** and it **shows your prescribed dose.** (See figure I).	I 
The dashed line ( ) in the dose counter will guide you to your dose. The dose selector clicks differently when turned forward, backwards or past your dose. You will hear a 'click' every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear. (See figure J).	J  **Dashed line**
When your prescribed dose lines up with the dose pointer, you have selected your dose. In this picture, the dose **0.25 mg** is shown as an example. If the dose counter stops before you reach your prescribed dose, see the section **'Do you have enough Kayshild?'** below these instructions. (See figure K).	K  **Example: 0.25 mg selected**

Choose your injection site

Choose upper arms, upper legs or stomach (keep a 5 cm distance from your belly button).

You may inject in the same body area each week, but make sure it is not in the same spot as used the last time.



3. Inject your dose

Insert the needle into your skin.

Make sure you can see the dose counter. Do not cover it with your fingers. This could interrupt the injection.

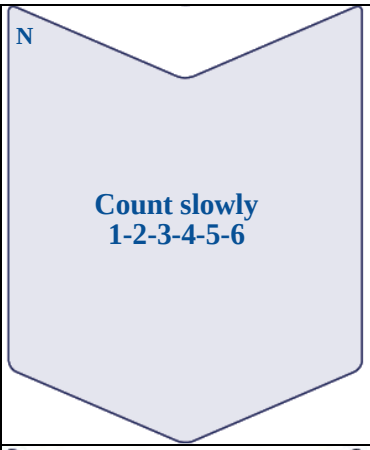
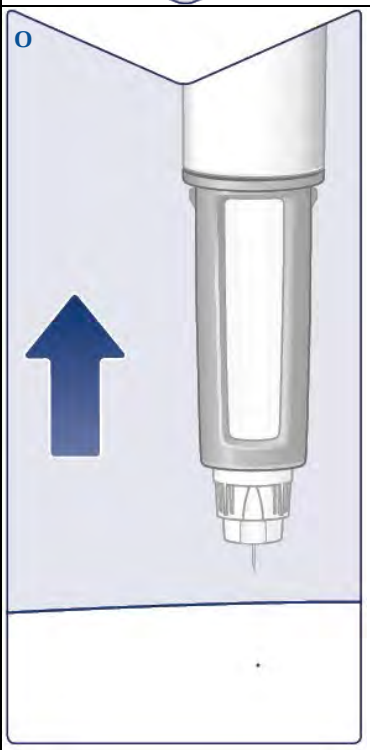
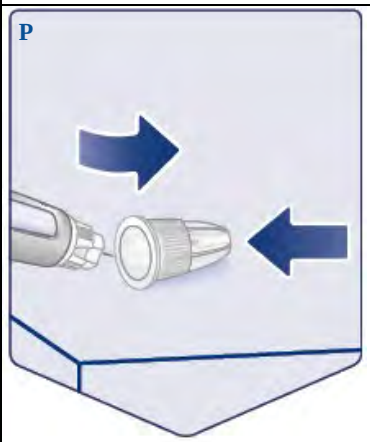
(See figure L).

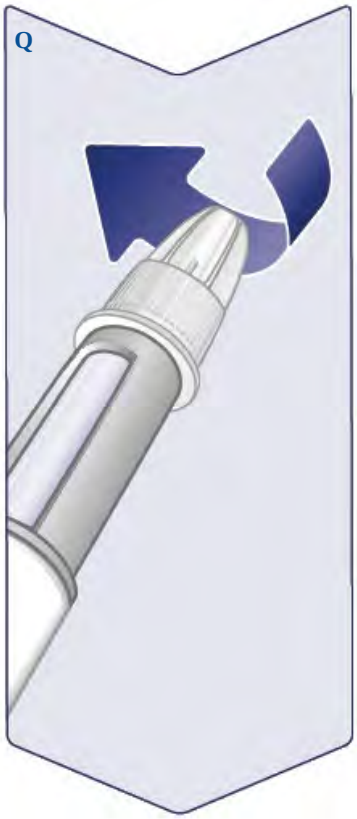
Press and hold down the dose button until the dose counter shows 0.

(See figure M).

Keep pressing the dose button with the needle in your skin and slowly count to 6. The 0 must line up with the dose pointer. You may hear or feel a click when the dose counter returns to 0.

(See figure N).

	
Remove the needle from your skin. If the needle is removed earlier, a stream of Kayshild may 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 Kayshild at the needle tip after injecting. This is normal and does not affect your dose. (See figure O).	
4. After your injection	
Lead the needle tip into the outer needle cap on a flat surface without touching the needle or the outer needle cap. **Once the needle is covered,** carefully push the outer needle cap completely on. (See figure P).	

Unscrew the needle and dispose of it carefully as instructed by your doctor, nurse, pharmacist or local authorities. **Never try to put the inner needle cap back on the needle.** You may stick yourself with the needle. **Always 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.** (See figure Q).	
Put the pen cap on your pen after each use to protect Kayshild from light. (See figure R).	
When the pen is empty, dispose of the pen without a needle on as instructed by your doctor, nurse, pharmacist or local authorities. The pen cap and the empty carton can be disposed of in your household waste.	
About your needles	

How to identify a blocked or damaged needle

- If -0- does not appear in the dose counter after continuously pressing the dose button, you may have used a blocked or damaged needle.
- In this case, you have **not** received any Kayshild – even though the dose counter has moved from the original dose that you have set.

How to handle a blocked needle

Change the needle as instructed in **'1. Prepare your pen with a new needle'** and go to **'2. Set your dose'.**

Caring for your pen

Treat your pen with care. Rough handling or misuse may cause inaccurate dosing.
If this happens, you might not get the intended effect of Kayshild.

- See the back of this leaflet to read the storage conditions for your pen.
- **Do not inject Kayshild that has been exposed to direct sunlight.**
- **Do not subject Kayshild to frost and never inject Kayshild that has been frozen.** Dispose of the pen.
- **Do not drop your pen** or knock it against hard surfaces.
- **Do not try to refill your pen.** Once empty, it must be disposed of.
- **Do not try to repair your pen** or pull it apart.
- **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.

Do you have enough Kayshild?

If the dose counter stops before you reach your prescribed dose, there is not enough Kayshild left for a full dose. Dispose of the pen and use a new Kayshild pen.

Important information

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

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.