PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Fiasp®

insulin aspart injection

Solution, 100 U/mL, Subcutaneous use

House Standard

Antidiabetic Agent

ATC Code: A10AB05

fast-acting

Novo Nordisk Canada Inc.
101-2476 Argentia Road.
Mississauga, Ontario
Canada, L5N 6M1

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RECENT MAJOR LABEL CHANGES

Indications, General (1)	FEB 2020
Indications, Pediatrics (1.1)	FEB, 2020
Dosage and Administration, Administration (4.3)	FEB, 2020
Dosage and Administration, Recommended Dose and Dosage Adjustment (4.2)	FEB, 2020
Warnings and Precautions, Pediatrics (8.1.3)	FEB 2020
Adverse Reactions, Clinical Trial Adverse Reactions (9.2)	FEB 2020
Clinical Trials, Study Results (15.2)	FEB 2020

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Fiasp® (insulin aspart injection) is indicated for treatment of adult and pediatric patients (>2 years old) with diabetes mellitus who require mealtime insulin for the control of hyperglycemia (see CLINICAL TRIALS).

Fiasp® should generally be used in a regimen with intermediate- or long-acting insulin (plus metformin for type 2 diabetes as recommended) to maintain adequate glucose control (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

Fiasp® (10 mL vials) may also be used for continuous subcutaneous insulin infusion (CSII) in pump systems that are licenced in Canada for insulin infusion. Refer to the insulin infusion pump manufacturers' user manual to see if Fiasp® can be used.

1.1 Pediatrics

Pediatrics (< 18 years of age): Fiasp® can be used in pediatric patients aged 2 years and above. There is no clinical experience with the use of Fiasp® in pediatric patients with type 1 diabetes mellitus below the age of 2 years or in patients with type 2 diabetes mellitus below the age of 18 years.

1.2 Geriatrics

Geriatrics (> 65 years of age): There is limited evidence available in elderly patients with type 1 diabetes. In elderly patients with type 2 diabetes, no overall differences in efficacy or safety were observed between the elderly and younger adult patients (see 7 WARNINGS AND PRECAUTIONS, Geriatrics).

2 CONTRAINDICATIONS

Insulin aspart is contraindicated:

- In patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- During episodes of hypoglycemia (see 7 WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin products. As with all insulin products, the timing of hypoglycemia may differ. Glucose monitoring shall be performed for all patients with diabetes mellitus treated with insulins. (See 7 WARNINGS AND PRECAUTION, Hypoglycemia, Hyperglycemia and 5 OVERDOSAGE).
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death. (See 7 WARNINGS AND PRECAUTION, Hypoglycemia).
- Any conversion of insulin products should be made cautiously and only under medical

supervision. (See 6 DOSING AND ADMINSTRATION).

- Due to its rapid onset of action and shorter duration of action, Fiasp® should be injected up to 2 minutes before the start of the meal. When necessary, Fiasp® may be administered up to 20 minutes after starting the meal (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).
- DO NOT dilute or mix Fiasp® with any other insulin products or solutions, except I.V. infusion fluids under medical supervision.
- Fiasp® should generally be used in a regimen with intermediate- or long-acting insulin (plus metformin for type 2 diabetes as recommended) or with insulin infusion pump therapy to maintain adequate glucose control (see 6 DOSAGE AND ADMINISTRATION).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The potency of insulin analogues, including Fiasp®, is expressed in units. One (1) unit of Fiasp® corresponds to 1 international unit of human insulin or 1 unit of other fast-acting insulin analogues.
- Always check insulin label before administration (see 7 WARNINGS AND PRECAUTIONS).
- Inspect visually for particulate matter and discolouration. Only use Fiasp® if the solution appears water-clear and colourless.
- Fiasp® in a vial is to be used with insulin syringes or in Continuous Subcutaneous Insulin Infusion (CSII) therapy with the corresponding unit scale (U-100 or 100 U/mL).
- Train patients on proper use and injection technique before initiating Fiasp®. Training reduces the risk of administration errors such as needle sticks and incomplete dosing.
- Inject Fiasp® subcutaneously into the abdomen, upper arm, or thigh.
- Always rotate injection sites within the same region from one injection to the next so that the same site is not used more than approximately once a month to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Fiasp® should not be injected into areas of lipodystrophy or localized cutaneous amyloidosis (see 8 ADVERSE REACTIONS).
- DO NOT dilute or mix Fiasp® with any other insulin products except I.V. infusion fluids under medical supervision.
- Before travelling between different time zones, the patient should seek the advice of a health professional since this means the patient has to take insulin and meals at different times.
- The dosage of Fiasp® must be individualized. Individualize and titrate the dose of Fiasp® based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal (see 7 WARNINGS AND PRECAUTIONS).
- Dose adjustments may be needed with switching from another insulin, changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in concomitant medications, changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia (see 7 WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

Starting Dose in Insulin-Naïve Patients

Type 1 Diabetes Mellitus
Fiasp® is to be used as mealtime insulin and requires subsequent individual dosage adjustments.

The recommended starting dose of Fiasp® in insulin naïve adult patients with type 1 diabetes is approximately 50% of the total daily insulin dose and should be divided between each daily meal. The remainder of the total daily insulin dose should be administered as intermediate- or long-acting insulin. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin naïve patients with type 1 diabetes.

Type 2 Diabetes Mellitus
The suggested initial dose for adult patients is 4 units at one or more meals. The number of injections and subsequent titration will depend on individual glycemic targets.

Pediatric Patients
Dosage of Fiasp® in newly diagnosed pediatric patients with type 1 or type 2 diabetes should be individualized and determined based on the physician's advice in accordance with the needs of the patient. Pediatric patients treated with Fiasp® should be carefully monitored for hypoglycemia.

Converting to Fiasp® from other insulin therapies in patients with either type 1 or type 2 diabetes
Close glucose monitoring is recommended when converting from other mealtime insulins and in the initial weeks thereafter.

If converting from another mealtime insulin to Fiasp®, the change can be done on a unit-to-unit basis (see CLINICAL TRIALS). Due to the faster onset of insulin action, Fiasp® should be injected at the start of a meal. When necessary, Fiasp® may be administered up to 20 minutes after starting the meal (see CLINICAL TRIALS).

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

Doses and timing of concurrent intermediate- or long-acting insulin or other concomitant antidiabetic treatment may need to be adjusted.

Patients with type 2 diabetes mellitus
Fiasp® adjustment may be considered daily based on mealtime and bedtime Self-monitoring Blood Glucose (SMBG) on the previous day according to Table 1.

- Pre-breakfast Fiasp® should be adjusted according to the pre-lunch SMBG the previous day
- Pre-lunch Fiasp® should be adjusted according to the pre-dinner SMBG the previous day
- Pre-dinner Fiasp® should be adjusted according to the bedtime SMBG the previous day

Table 1 Dose adjustment based on mealtime or bedtime plasma glucose

Dose adjustment	
Mealtime or bedtime plasma glucose	**Dose adjustment**
mmol/L	Unit

< 4.0	-1
4.0 - 6.0	No adjustment
> 6.0	+1

4.4 Administration

Subcutaneous Injection:

- Fiasp® is a mealtime insulin for subcutaneous administration up to 2 minutes before the start of the meal. When necessary, Fiasp® may be administered, up to 20 minutes after starting the meal (see CLINICAL TRIALS).
  Fiasp® given by subcutaneous injection should generally be used in regimens with intermediate- or long-acting insulin (plus metformin for type 2 diabetes as recommended). See 7 WARNINGS AND PRECAUTIONS. The individual total daily insulin requirement in adults, adolescents and children may vary and is usually between 0.5 and 1.0 unit/kg/day. In a basal-bolus treatment regimen approximately 50% of this requirement may be provided by Fiasp® and the remainder by intermediate- or long-acting insulin.
- Patients on basal-bolus treatment who forget a mealtime dose are advised to monitor their blood glucose level to decide if an insulin dose is needed. Patients should resume their usual dosing schedule at the next meal.

Continuous Subcutaneous Infusion (Insulin Infusion Pump) with the 10 mL vial:

- Fiasp® can be used for CSII in pumps suitable for CSII and will cover both the bolus insulin requirement (approximately 50%) and the basal insulin requirement. Use Fiasp® in accordance with the insulin infusion pumps' instructions for use.
- Train patients using continuous subcutaneous insulin infusion pump therapy to administer insulin by injection and have alternate insulin therapy available in case of pump failure.
- Administer Fiasp® by continuous subcutaneous infusion into the subcutaneous tissue of the abdominal wall. Rotate infusion sites within the same region to reduce the risk of lipodystrophy and localized cutaneous amyloidosis (see 8 ADVERSE REACTIONS).
- Change the infusion set and the infusion set insertion site according to the insulin infusion pump manufacturers' user manual.
- Change Fiasp® in the pump reservoir at least every 6 days, or according to the pump user manual, whichever is shorter.
- Do NOT dilute or mix Fiasp® when administering by continuous subcutaneous infusion.
- Do NOT expose Fiasp® in the pump reservoir to temperatures greater than 37°C (98.6°F).

Intravenous (IV) Administration:

- Fiasp® can be administered IV under medical supervision for glycemic control with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia.
- Fiasp® should be used at concentrations from 0.5 unit/mL to 1.0 unit/mL insulin aspart in infusion systems using polypropylene infusion bags.
- Fiasp® has been shown to be stable at room temperature for 24 hours in IV infusion fluids such as 0.9% sodium chloride or 5% dextrose.
- Care should be taken to ensure that the insulin is injected into the IV infusion bag and not simply the entry port.

4.5 Missed Dose

Patients on basal-bolus treatment who forget a mealtime dose are advised to monitor their blood glucose level to decide if an insulin dose is needed. When necessary, Fiasp® may be given up to 20 minutes after starting a meal and then patients should resume their usual dosing schedule at the next meal.

5 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. An excess of insulin relative to food intake, energy expenditure, or both, may lead to severe and life-threatening hypoglycemia and hypokalemia (see 7 WARNINGS AND PRECAUTIONS). Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure or neurologic impairment may be treated with intramuscular/ subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Description

Fiasp® is a mealtime fast-acting insulin aspart formulation. Insulin aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*.

Fiasp® is an aqueous sterile, clear and colourless solution of insulin aspart.

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	• Pack size for vial is 1 x 10 mL. • Pack size for 3 mL Penfill® cartridge 5 x 3 mL. • Pack size for 3 mL FlexTouch® (pre-filled pen) 5 x 3 mL	glycerol, phenol, metacresol, zinc, disodium phosphate dihydrate, arginine hydrochloride, niacinamide (vitamin B_3) and water for injections. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

Fiasp® is available as a water-clear and colourless solution for injection in 10 mL vials, in 3 mL Penfill® cartridges, and in 3 mL Fiasp® FlexTouch® disposable pens.

Fiasp® Penfill® cartridges are designed for use with Novo Nordisk Insulin Delivery Devices and NovoFine®, NovoFine® Plus and NovoTwist® needles. Fiasp® FlexTouch® (pre-filled pens) are designed for use with NovoFine®, NovoFine® Plus and NovoTwist® needles.

Active ingredients: 1 mL of the solution contains 100 Units of insulin aspart (equivalent to 3.5 mg).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

As with all insulins, the duration of action of Fiasp® may vary in different individuals or in the same individual according to dose, injection site, blood flow, temperature and level of physical activity.

Stress or concomitant illness, especially infectious and febrile conditions may change insulin requirements. In these instances, patients should contact their physician and carefully control their blood glucose.

Thiazolidinediones (TZDs), alone or in combination with other anti-diabetic agents (including insulin), can cause heart failure and oedema. The combination of insulin with a TZD is not indicated for the treatment of type 2 diabetes mellitus. Please refer to the respective TZD product monograph, (see 7 WARNINGS AND PRECAUTIONS), information when the use of these drugs in combination with any insulin, including Fiasp®, is contemplated.

There is limited clinical experience with rapid acting insulins used in combination with a GLP-1 receptor agonist.

Fiasp® FlexTouch®, Penfill® or a Novo Nordisk Insulin Delivery Device should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

Antibody production

As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form. The presence of such antibodies may necessitate adjustment of the insulin dose to correct for tendencies toward hyper- or hypoglycemia.

In a 26-week, active-controlled study of type 1 diabetes patients (N=1143), most subjects had insulin antibodies due to previous insulin treatment, at baseline. The mean level of total insulin aspart antibodies was 14.0 %B/T at baseline and 18.2 %B/T at the end of the trial for mealtime Fiasp®; the change from baseline was similar across the three treatment groups, mealtime Fiasp®, post-meal Fiasp® and mealtime NovoRapid®.

In a 26-week, active-controlled study of pediatric type 1 diabetes patients (N=777), the mean

level of total insulin aspart antibodies was 20.2 %B/T at baseline and 16.8 %B/T at the end of treatment for mealtime Fiasp®; the change from baseline was similar across the three treatment groups, mealtime Fiasp®, post-meal Fiasp® and mealtime NovoRapid®.

Avoidance of accidental mix-ups/medication errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between Fiasp® and other insulin products.
Patients must visually verify the units of the dose prior to administering Fiasp®. Therefore, the requirement for patients to self-administer is that they can read the dose scale. Patients, who are blind or have poor vision, must be instructed to always get assistance from another person who has good vision and is trained in administration of insulins.

Endocrine and Metabolism

Hypoglycemia

As with other insulins, hypoglycemia is the most common adverse reaction of insulin therapy, including Fiasp® (see 8 ADVERSE REACTIONS). Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Patients, whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with long-standing diabetes. Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see 8 ADVERSE REACTIONS, Hypoglycemia and 5 OVERDOSAGE).

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

Hypoglycemia can occur regardless of what type of insulin you take and can cause fatigue, sweating, heart palpitations, disturbed behavior, hunger, convulsions, loss of consciousness temporary or permanent impairment of brain function, or, in extreme circumstances, even death which can occur without recognizable symptoms.

Some people may not recognize when their blood sugar drops low.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. Fiasp® has a distinct time action profile (see Pharmacokinetics), which impacts the timing of hypoglycemia. A consequence of the pharmacodynamics of Fiasp® is that if hypoglycemia occurs, it may occur earlier after an injection when compared to other mealtime insulins.

Fiasp® should be administered up to 2 minutes before the start of the meal. When necessary, Fiasp® may be administered up to 20 minutes after starting the meal (see CLINICAL TRIALS); the fast onset of action should therefore be considered in patients with delayed gastric emptying.

Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland may require changes in the insulin dose.

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

Hyperglycemia
The use of inadequate doses or discontinuation of treatment, especially in patients requiring insulin, may lead to hyperglycemia and diabetic ketoacidosis; conditions which are potentially lethal.

Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction
Pump or infusion set malfunctions can lead to a rapid onset of hyperglycemia and ketoacidosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection of Fiasp® may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure (see 4 DOSAGE AND ADMINISTRATION, and 11 STORAGE, STABILITY AND DISPOSAL).

Fertility
Animal reproduction studies have not revealed any differences between insulin aspart and human insulin regarding fertility.

Hypokalemia
All insulin products, including Fiasp®, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia [e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations, patients receiving intravenously administered insulin, or patients losing potassium through other means (e.g., diarrhea)] (see 5 OVERDOSAGE).

Immune
Local allergic reaction
As with any insulin therapy, patients may experience rash, redness, itching, bruising or inflammation at the site of Fiasp® injection (see 8 ADVERSE REACTIONS). Most of these reactions usually resolve in a few days to a few weeks. They may occur if the injection is not properly made (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to the insulin or any excipients (see 2 CONTRAINDICATIONS). Localized reactions and generalized myalgias have been reported with injected metacresol which is an excipient of Fiasp®. On rare occasions, injection site reactions may require discontinuation of Fiasp®.

Lipodystrophy and Cutaneous Amyloidosis
SC administration of insulin products, including Fiasp® can result in lipoatrophy (thinning of adipose tissue) or lipohypertrophy (thickening of adipose tissue) or localized cutaneous amyloidosis (skin lumps) which may affect insulin absorption.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. Patients should be advised to consult their health professional if they notice any of these conditions and before changing the

injection site. There is a potential risk of delayed insulin absorption and worsened glycemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

Systemic Allergic Reaction
Systemic allergic reactions have rarely occurred with Fiasp® as with other insulin treatment. These reactions may be characterized by a generalized rash (with pruritus), shortness of breath, wheezing and drop in blood pressure. Severe cases of generalized allergy including anaphylactic reaction may be life threatening. If hypersensitivity reactions occur, discontinue Fiasp®; treat per standard of care and monitor until symptoms and signs resolve.

Insulin initiation and glucose control intensification
Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, acute painful peripheral neuropathy, and peripheral oedema. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Monitoring and Laboratory Tests
As with all insulin therapy, the need for regular blood glucose self-monitoring should be considered when using Fiasp® to obtain optimal glycemic control. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control. If a patient is pregnant, careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Mixing of insulins: DO NOT dilute or mix Fiasp® with any other insulin products or solutions, except I.V. infusion fluids under medical supervision.

Other
The presence of diseases such as acromegaly, Cushing's syndrome, hyperthyroidism and pheochromocytoma can complicate the control of diabetes mellitus.

Renal and Hepatic Impairment
Renal or hepatic impairment may reduce the patient's insulin requirements. In patients with renal or hepatic impairment, glucose monitoring should be intensified and the dose adjusted on an individual basis.

Patients with mild impaired renal function and a limited number of patients with moderate impaired renal function or impaired liver function were included in the controlled clinical studies. Therefore, the safety profile in patients with hepatic impairment and in patients with moderate to severe renal impairment is limited. See 10 CLINICAL PHARMACOLOGY.

7.1 Special Populations

7.1.1 Pregnant Women

Fiasp® has not been studied in pregnancy. Patients should be advised to discuss with their health care provider if they intend to or if they become pregnant. Fiasp® should be used during

pregnancy only if the potential benefit justifies the potential risk to the fetus. For studies in animals, see 16 NON-CLINICAL TOXICOLOGY.

Intensified blood glucose control and monitoring of pregnant women with diabetes or a history of gestational diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements normally return rapidly to pre-pregnancy values. Careful monitoring of glucose control is essential in these patients.

7.1.2 Breast-feeding

It is unknown whether Fiasp® is excreted in significant amounts in human milk. For this reason, caution should be exercised when Fiasp® is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan or both.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of Fiasp® in diabetes mellitus has been established in pediatric patients 2 years of age and older. Fiasp® has not been studied in pediatric patients with type 1 diabetes mellitus younger than 2 year of age or in patients with type 2 diabetes mellitus below the age of 18 years.

Close monitoring of blood glucose levels is recommended if administering this medicine after the start of the last meal of the day, in order to avoid nocturnal hypoglycemia.

7.1.4 Geriatrics

Geriatrics (> 65 years of age):

Type 1 Diabetes:

There is limited evidence available in elderly patients with type 1 diabetes. In a controlled clinical study, 58 of 763 (0.08%) Fiasp® treated patients with type 1diabetes were ≥65 years of age, of which 7 patients were ≥75 years of age.

Type 2 Diabetes:

In two controlled clinical studies, 133/456 (29%) Fiasp® treated patients with type 2 diabetes were ≥65 years of age and 17/456 (3.7%) were ≥75 years of age. No overall differences in safety or efficacy were observed between these elderly patients and younger adult patients.

As with all insulins, caution should be exercised when Fiasp® is administered to geriatric patients. In geriatric patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be more difficult to recognize in the elderly. See 7 WARNINGS AND PRECAUTIONS, hypoglycemia, 8 ADVERSE REACTIONS and CLINICAL TRIALS.

A pharmacokinetic/pharmacodynamic study to assess the effect of age on the onset of Fiasp® action has been performed**.** See 10 CLINICAL PHARMACOLOGY.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse reactions are also discussed elsewhere:

- Hypoglycemia (see 7 WARNINGS AND PRECAUTIONS)
- Allergic reactions (see 7 WARNINGS AND PRECAUTIONS)

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data in Table 2 reflect the exposure of 763 adult patients with type 1 diabetes to Fiasp® during a 26-week active-controlled trial (Study 3852) with a mean duration of 25.3 weeks. The type 1 diabetes population had the following characteristics: Mean age was 44.4 years and mean duration of diabetes was 19.9 years. 59% were male, 93.3% were Caucasian, 2.3% were African American and 6.9% were Hispanic. The mean BMI was 26.7 kg/m^2. Mean HbA_{1c} at baseline was 7.61%.

The data in Table 3 reflect the exposure of 341 adult patients with type 2 diabetes to Fiasp® during a 26-week active-controlled trial (Study 3853) with a mean duration of 24.5 weeks. The type 2 diabetes population had the following characteristics: Mean age was 59.6 years and mean duration of diabetes was 13.2 years. 47.2% were male, 80.3% were Caucasian, 6.4% were African American and 7.5% were Hispanic. The mean BMI was 31.5 kg/m^2. Mean HbA_{1c} at baseline was 7.96%.

Table 2 Adverse Reactions in Adult Patients with Type 1 Diabetes (incidence ≥ 1%)

	Mealtime Fiasp®+ Insulin detemir N=386 (%)	**Postmeal Fiasp®+ Insulin detemir N=377 (%)**	**NovoRapid® + Insulin detemir N=380 (%)**
Severe or BG confirmed hypoglycemia*	358 (92.7)	358 (95.0)	370 (97.4)
Severe hypoglycemia**	26 (6.7)	30 (8.0)	32 (8.4)
Allergic skin manifestations	12 (3.1)	6 (1.6)	6 (1.6)
Injection site reactions***	7 (1.8)	9 (2.4)	3 (0.8)

*Confirmed hypoglycemia (Novo Nordisk classification) includes the episodes where a subject was unable to treat himself/herself and/or have a recorded BG <3.1 mmol/L
**Severe hypoglycemia (American Diabetes Association - ADA classification): an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions
***Incidence rates related to both basal and bolus insulin injection

Table 3 Adverse Reactions in Adult Patients with Type 2 Diabetes (incidence ≥ 1%)

	Fiasp® + Insulin glargine N=341 (%)	NovoRapid® + Insulin glargine N=341 (%)
Severe or BG confirmed hypoglycemia*	262 (76.8)	250 (73.3)
Severe hypoglycemia**	11 (3.2)	13 (3.8)

*Confirmed hypoglycemia (Novo Nordisk classification) includes the episodes where a subject was unable to treat himself/herself and/or have a recorded BG <3.1 mmol/L
**Severe hypoglycemia (ADA classification): an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions

The data in Table 4 reflect the exposure of 236 adult patients with type 1 diabetes to Fiasp® in a continuous subcutaneous insulin infusion (CSII) during a 16-week active-controlled trial (Study 3854) with a mean duration of 16.0 weeks. The type 1 diabetes population using CSII had the following characteristics: Mean age was 43.5 years and mean duration of diabetes was 24.2 years. 43.0% were male, 88.8% were Caucasian, 1.5% were African American and 2.8% were Hispanic. The mean BMI was 26.33 kg/m^2. Mean HBA_{1c} at baseline was 7.49%.

Table 4 Adverse Reactions in Adult Patients with Type 1 Diabetes using CSII (incidence ≥ 1%)

	Fiasp® N=236 (%)	NovoRapid® N=236 (%)
Severe or BG confirmed hypoglycemia*	231 (97.9)	228 (96.6)
Severe hypoglycemia**	11 (4.7)	5 (2.1)
Infusion site reaction	24 (10.2)	21 (8.9)
Allergic reactions	10 (4.2)	7 (3.0)

*Confirmed hypoglycemia (Novo Nordisk classification) includes the episodes where a subject was unable to treat himself/herself and/or have a recorded BG <3.1 mmol/L
**Severe hypoglycemia (ADA classification): an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions

The data in Table 5 reflect the exposure of 519 pediatric patients with type 1 diabetes to Fiasp® during a 26-week, active-controlled trial (Study 4101) with a mean duration of 25.7 weeks. The pediatric type 1 diabetes population had the following characteristics: Mean age was 11.68 years and mean duration of diabetes was 4.38 years. 53.9% were male, 81.3% were Caucasian, 1.9% were African American and 5.8% were Hispanic. The mean BMI was 19.66 kg/m^2. Mean HBA_{1c} at baseline was 7.56%.

Table 5 Adverse Reactions in Pediatric Patients with Type 1 Diabetes (incidence ≥ 1%)

	Mealtime Fiasp® + insulin degludec N=260 (%)	Postmeal Fiasp® + insulin degludec N=259 (%)	Mealtime NovoRapid® + insulin degludec N=258 (%)
Severe or BG confirmed hypoglycemia*	228 (87.4)	227 (88.0)	217 (84.1)

Severe hypoglycemia**	3 (1.1)	8 (3.1)	4 (1.6)
Injection site reactions***	8 (3.1)	14 (5.4)	11 (4.3)
Lipodystrophy	7 (2.7)	4 (1.6)	4 (1.6)
Allergic reactions	13 (5.0)	8 (3.1)	9 (3.5)

*Severe or BG confirmed: Severe according to the ISPAD 2014 classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
**Severe hypoglycemia: Severe according to the ISPAD 2014 classification
***Incidence rates related to both basal and bolus insulin injection

Hypoglycemia
Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including Fiasp® (see 7 WARNINGS AND PRECAUTIONS).

Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentrating, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

The percentage of participants randomized to Fiasp® who experienced at least one episode of hypoglycemia in clinical trials in adult patients with type 1 and type 2 diabetes are shown in Table 2 and Table 3, respectively, and the percentage of participants randomized to Fiasp® who experienced at least one episode of hypoglycemia in clinical trials in adult patients with type 1 diabetes using CSII is shown in Table 4. The percentage of participants randomized to Fiasp® who experienced at least one episode of hypoglycemia in clinical trials in pediatric patients with type 1 diabetes is shown in Table 5. Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. A confirmed hypoglycemia episode was defined as a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 3.1 mmol/L (i.e., with or without the presence of hypoglycemic symptoms).

Allergic Reactions
Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including Fiasp®, and may be life threatening (see 7 WARNINGS AND PRECAUTIONS).

In the clinical program (n=1244), generalized hypersensitivity reactions (manifested by generalized skin rash and facial edema) were reported in 0.2% of adult patients treated with Fiasp®. Allergic skin manifestations reported with Fiasp® in 1.5% of adult patients from the clinical program include eczema, rash, rash pruritic, urticaria and dermatitis.

In the CSII study, allergic reactions were reported in 4.2% of adult patients with type 1 diabetes treated with Fiasp®.

Skin and subcutaneous tissue disorders
Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. In the clinical program (n=1244), lipodystrophy was reported at the injection/infusion site in patients treated with Fiasp® (0.5% vs. 0.2% in comparator) (see 7 WARNINGS AND PRECAUTIONS).

Injection/Infusion Site Reactions
As with other insulin therapy, patients may experience rash, redness, inflammation, pain, bruising or itching at the site of Fiasp® injection or infusion. In the clinical program (n=1219), injection site reactions occurred in 1.5% of adult patients treated with Fiasp®. In the pump clinical program, adult patients with type 1 diabetes treated with Fiasp® in a pump reported 10.0% infusion site reactions (vs. 8.3% in the NovoRapid® group).

Weight Gain
Weight gain has occurred with insulin therapies including Fiasp® and has been attributed to the anabolic effect of insulin. In the clinical program, after 26 weeks of treatment, adult patients with type 1 diabetes (Study 3852) treated with mealtime Fiasp® gained an average of 0.67 kg and adult patients with type 2 diabetes gain an average of 2.68 kg (see CLINICAL TRIALS). In the type 2 diabetes population (Study 3853), the adverse event 'weight increased' assessed by the investigator as possibly or probably related to Fiasp® was reported in 7 (2.1%) adult patients.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Safety and efficacy have been investigated in a therapeutic confirmatory trial in children with type 1 diabetes mellitus aged 2 to less than 18 years. In the trial, 519 pediatric patients were treated with Fiasp®. Overall the frequency, type and severity of adverse reactions in the pediatric population do not indicate differences to the experience in the adult population. Lipodystrophy (including lipohypertrophy, lipoatrophy) at the injection site was reported more often in pediatric patients compared to adults. For lipodystrophy in the pediatric population please see table 5.

Monitor blood glucose levels closely in pediatric patients (see CLINICAL TRIALS).

8.3 Less Common Clinical Trial Adverse Reactions

In addition, the following adverse events were assessed as possibly or probably related by investigator at an incidence of <1% for Fiasp® in the clinical program.

- **Cardiac disorders:** palpitations
- **Congenital, familial and genetic disorders:** colour blindness
- **Eye disorders:** vision blurred
- **Gastrointestinal disorders:** nausea and faeces hard
- **General disorders and administration site conditions:** injection site bruising, injection site erythema, injection site haematoma, injection site hypertrophy, infusion site induration, infusion site pruritus and injection site reaction, asthenia, fatigue, hunger, local swelling, oedema and oedema peripheral.
- **Immune system disorders:** hypersensitivity
- **Infections and infestations:** nasopharyngitis
- **Injury, poisoning and procedural complications:** accidental overdose, extra dose administered and fall
- **Investigations:** weight increased, platelet count decreased, urine albumin/creatinine ratio increased and liver function test abnormal
- **Metabolism and nutrition disorders:** diabetes mellitus, hyperglycemia and overweight

- **Musculoskeletal and connective tissue disorders:** myalgia, joint swelling and musculoskeletal pain
- **Neoplasms benign, malignant and unspecified (incl cysts and polyps):** cardiac myxoma
- **Nervous system disorders:** hypoglycemic unconsciousness, dizziness and neuroglycopenia
- **Psychiatric disorders:** disorientation and anxiety
- **Respiratory, thoracic and mediastinal disorders:** pulmonary embolism (with fatal outcome)
- **Skin and subcutaneous tissue disorders:** pruritus, lipodystrophy acquired, skin mass and ecchymosis

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

See 8.2.1 Clinical Trial Adverse Reactions – Pediatrics.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

A number of medicinal products are known to interact with the glucose metabolism. Therefore an increased frequency of glucose monitoring may be required when Fiasp® is co-administered with these drugs.

The following substances may reduce insulin requirement:
Antidiabetic agents (GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors), ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.

The following substances may increase insulin requirement:
Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
The following substances may reduce or increase insulin requirement:
Octreotide/lanreotide, alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The following substances may mask the symptoms of hypoglycemia:
Beta-blockers, clonidine, guanethidine, and reserpine.

Other:
To avoid the risk of developing new or worsening heart failure, the use of thiazolidinediones (TZDs) in combination therapy with insulin is not indicated (See 7 WARNINGS AND PRECAUTIONS).

9.5 Drug-Food Interactions

Please refer to 10.1 CLINICAL PHARMACOLOGY, Mechanism of Action and 6 DOSAGE AND ADMINISTRATION for interactions with food and timing of food consumption, respectively.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The primary activity of Fiasp® is the regulation of glucose metabolism. Insulins, including insulin aspart, the active ingredient in Fiasp®, exert their specific action through binding to insulin receptors. Receptor-bound insulin lowers blood glucose by facilitating cellular uptake of glucose into skeletal muscle and adipose tissue and by inhibiting the output of glucose from the liver.

10.2 Pharmacodynamics

Pharmacodynamic results from three euglycemic clamp trials conducted in adult patients with type 1 diabetes showed the onset of action was 5 minutes earlier and time to maximum glucose infusion rate was approximately 11 minutes shorter with Fiasp® than with NovoRapid®.

The duration of action was shorter and the late glucose lowering effect was 10% smaller for Fiasp® compared to that of NovoRapid®. The total ($AUC_{GIR\ (0\text{-}12h)}$) and maximum ($GIR_{max}$) glucose lowering effect were comparable between Fiasp® and NovoRapid®, Total and maximum glucose lowering effect of Fiasp® increased linearly with increasing dose within the therapeutic dose range.

The day-to-day variability within-patients in glucose-lowering-effect was low for Fiasp® both for early ($AUC_{GIR,\ 0\text{-}1h}$, CV~26%), total ($AUC_{GIR,\ 0\text{-}12h}$, CV~18%) and maximum glucose lowering effect (GIR_{max}, CV 19%).

In standard biological assays in mice and rabbits, one unit of Fiasp® has the same glucose-lowering effect as one unit of NovoRapid®. In humans, the effect of Fiasp® is more rapid in absorption and onset of appearance, compared to NovoRapid®, due to its faster absorption after subcutaneous injection.

The duration of action of Fiasp® is between 3 and 5 hours. Fiasp® may be administered up to 20 minutes after starting a meal. A maximum effect occurs between 1 and 3 hours after the injection and the effect lasts for 3-5 hours.

10.3 Pharmacokinetics

Absorption

In healthy volunteers, after subcutaneous injection (0.2 U/kg), the absolute bioavailability of insulin aspart was approximately 80% after s.c. administration of fast-acting insulin aspart in the abdomen (83%), deltoid (77%) and thigh regions (77%).

The pharmacokinetics properties of Fiasp® were investigated in healthy volunteers and in patients with type 1 and type 2 diabetes mellitus.

Fiasp® is a mealtime insulin aspart formulation in which niacinamide (vitamin B_3) results in a faster initial absorption of insulin, leading to an earlier onset of exposure and greater early insulin exposure compared to NovoRapid®.

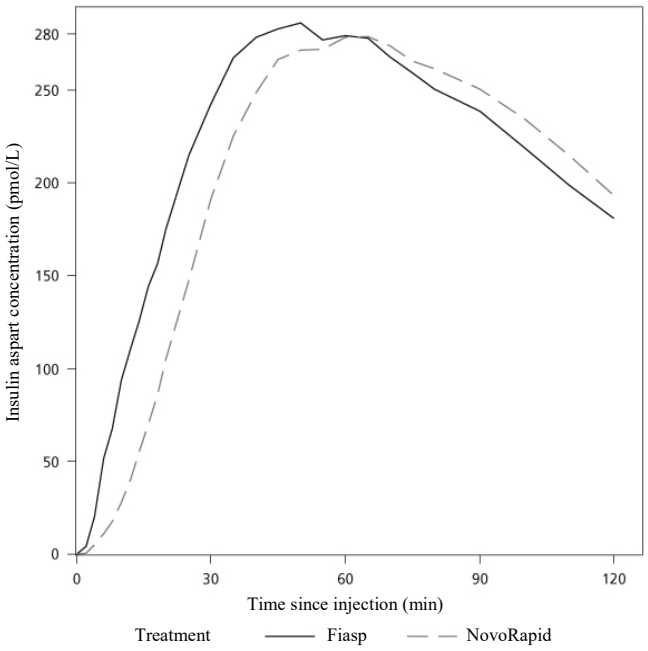


Figure 1 Mean insulin profile in adult patients with type 1 diabetes (0-2 hours) after subcutaneous injection (s.c.).

Pharmacokinetic results from six trials conducted in adult patients with type 1 diabetes showed that mean onset of appearance was approximately 4 minutes with Fiasp® and 9 minutes with NovoRapid®.

Table 6 shows the pharmacokinetic results from six trials conducted in adult patients with type 1 diabetes.

Table 6 Treatment ratio (Fiasp®/NovoRapid®) of insulin exposure

	Insulin exposure* **Subcutaneous injection**
Early insulin exposure	
$AUC_{insulin\ aspart,\ 0\text{-}15min}$	3.83 [3.41; 4.29]
$AUC_{insulin\ aspart,\ 0\text{-}30min}$	2.01 [1.87; 2.17]
$AUC_{insulin\ aspart,\ 0\text{-}1h}$	1.32 [1.26; 1.39]
$AUC_{insulin\ aspart,\ 0\text{-}1.5h}$	1.16 [1.12; 1.21]
$AUC_{insulin\ aspart,\ 0\text{-}2h}$	1.10 [1.06; 1.14]
Total insulin exposure	
$AUC_{insulin\ aspart,\ 0\text{-}12h}$	1.01 [0.98; 1.04]
$C_{max,\ insulin\ aspart}$	1.04 [1.00; 1.08]

The 95% confidence interval is stated in '[]'

*Based on free serum insulin aspart; AUC=area under the curve; Cmax=maximum observed concentration.

Distribution:

Insulin aspart has a low binding affinity to plasma proteins (<10%), similar to that seen with regular human insulin.

Elimination

Half-life after subcutaneous administration of Fiasp® is 57 minutes and comparable to NovoRapid®. Degradation of insulin aspart is similar to that of human insulin; all metabolites formed are inactive.

Special Populations and Conditions

- **Pediatrics**

In pediatric patients (6–18 years) with type 1 diabetes, Fiasp® showed an earlier onset of exposure and a higher early insulin exposure whilst maintaining a similar total exposure and maximum concentration compared to NovoRapid®.

Onset and early insulin exposure of Fiasp® was similar in pediatric patients (6-18 years) with type 1 diabetes to that in adult patients with type 1 diabetes. Total exposure of Fiasp® was lower in pediatric patients compared to adult patients when dosed with 0.2 units/kg body weight, while the maximum serum insulin aspart concentration was similar between age groups.

- **Geriatrics**

The pharmacokinetic properties of Fiasp® and NovoRapid® were investigated in a single dose study in 67 subjects (30 geriatric; 37 younger adults) with type 1 diabetes.

In geriatric patients with type 1 diabetes Fiasp® showed, an earlier onset of exposure and a higher early insulin exposure whilst maintaining a similar total exposure and maximum concentration compared to NovoRapid®.

- **Sex**

The effect of gender on the pharmacokinetics of Fiasp® was examined in an across-trial

analysis of the pharmacokinetic and pharmacodynamic studies. Fiasp® showed a comparable earlier onset of exposure and a higher early insulin exposure whilst maintaining a similar total exposure and maximum concentration compared to NovoRapid® for both female and male patients with type 1 diabetes.

- **Ethnic Origin**

The effect of race and ethnicity (African American versus Caucasian and Hispanics versus non-Hispanics) on the total insulin exposure of Fiasp® was explored in a cross-trial analysis of pharmacokinetic and pharmacodynamic studies conducted in patients with type 1 diabetes. For Fiasp®, no difference in exposure was found between the racial and ethnic groups investigated.

- **Hepatic Insufficiency**

The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of Fiasp® has not been studied (see WARNINGS AND PRECAUTIONS, Renal and Hepatic Impairment). However, the active substance, insulin aspart (NovoRapid®) in Fiasp® has been studied. A single subcutaneous dose of 0.06 unit/kg insulin aspart was administered in an open-label, single-dose study of 24 subjects (N=6/group) with different degrees of hepatic impairment (mild, moderate and severe) having Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment). In this small study, there was no correlation between the degree of hepatic impairment and any insulin aspart pharmacokinetic parameter.

- **Renal Insufficiency**

The effect of renal impairment on the total insulin exposure of Fiasp® was explored in a cross-trial analysis of pharmacokinetic and pharmacodynamic studies conducted in patients with type 1 diabetes. Renal function was defined using creatinine clearance (CLcr) as follows: ≥90 mL/min (normal) (N=546), 60-89 mL/min (mild) (N=115), 30-59 mL/min (moderate) (N=21). Higher total insulin exposure was observed with decreasing renal function for Fiasp®. However, there was some between subject variability in total insulin exposure across patients with type 1 diabetes with mild or moderate renal impairments. Thus, as with all insulin products, glucose monitoring should be intensified and the Fiasp® dosage adjusted on an individual basis in patients with renal impairment.

- **Obesity**

The effect of body mass index (BMI) on the pharmacokinetics of Fiasp® was explored in a cross-trial analysis of pharmacokinetic and pharmacodynamic studies. For patients with type 1 diabetes, the greater early insulin exposure for Fiasp® compared to NovoRapid® was preserved across BMI levels and this treatment difference increased with increasing BMI. Total and maximum insulin exposure was comparable between Fiasp® and NovoRapid® across BMI levels.

The effect of BMI on the total insulin exposure of Fiasp® was explored in a cross-trial analysis of pharmacokinetic and pharmacodynamic studies conducted in patients with type 1 diabetes. No relationship between total insulin exposure of Fiasp® and BMI was observed.

11 STORAGE, STABILITY AND DISPOSAL

Fiasp® should be stored between 2-8°C (36° to 46°F) in a refrigerator, but not in or near a freezing compartment. Fiasp® should not be exposed to heat or light. Do not freeze Fiasp® and do not use Fiasp® if it has been frozen. Fiasp® should not be drawn into a syringe and stored for later use.

Fiasp® Vials:

After initial use a vial may be kept at temperatures below 30°C (86°F) or in a refrigerator 2°C to 8°C (36°F to 46°F) for up to 28 days. Exposure to excessive heat and light must be avoided during use. Only use the product if it has a clear and almost colourless appearance.

Unpunctured vials can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

Fiasp® Penfill®:

After initial use, a Penfill® can be stored for up to 28 days. Do not store above 30°C (86°F). Penfill® must not be refrigerated. If cartridge is carried as a spare and unused, the cartridge should be kept in the carton in order to protect from light.

Fiasp® FlexTouch®:

Once a Fiasp® FlexTouch® is punctured, it can be stored for 28 days at room temperature below 30°C (86°F) or in a refrigerator 2°C to 8°C (36°F to 46°F), without the needle attached, but should not be exposed to excessive heat or light. Unpunctured Fiasp® FlexTouch® can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep the cap on the pen in order to protect from light. Keep unused Fiasp® FlexTouch® in the carton so they will stay clean and protected from light.

Always remove the needle after each injection and store Fiasp® FlexTouch® without a needle attached. This prevents contamination and/or infection, or leakage of insulin, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.

The storage conditions are summarized in Table 7.

Table 7 Storage conditions for Fiasp® vial, Penfill® and FlexTouch®

Fiasp® Presentation	**Not in-use (unopened)**		**In-use (opened)**	
	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)
10 mL Fiasp® vial	28 days	Until expiration date	28 days*	28 days*
3 mL Fiasp® Penfill®	28 days	Until expiration date	28 days	Do not refrigerate
3 mL Fiasp® FlexTouch®	28 days	Until expiration date	28 days	28 days

* For insulin infusion pump use, the total in-use time is 28 days, including 6 days pump in-use time

Storage of Fiasp® in Insulin Infusion Pumps:

To avoid insulin degradation, Fiasp® in the pump reservoir should be replaced:

- At least every 6 days, or according to the pump user manual, whichever is shorter

- After exposure to temperatures that exceed 37°C

The infusion set and infusion set insertion site should be changed according to the manufacturers' user manual.

Storage of Fiasp® in Infusion Fluids:

Infusion bags prepared as indicated under 4 DOSAGE AND ADMINISTRATION are stable at room temperature for 24 hours.

12 SPECIAL HANDLING INSTRUCTIONS

Penfill®/FlexTouch®: Needles and Fiasp® Penfill®/FlexTouch® must not be shared. The cartridge must not be refilled.

Fiasp® must not be used if it does not appear water-clear and colourless.

Fiasp® which has been frozen must not be used.

Penfill®/FlexTouch®: The patient should be advised to discard the needle after each injection.

Penfill®/FlexTouch®: In case of emergency in current Fiasp® users (hospitalisation or insulin pen malfunction), you should carry a spare insulin delivery device with a Penfill® or FlexTouch® and new needles with you.

Vial: Fiasp® may be used in an insulin infusion pump system (CSII). Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: insulin aspart injection

Chemical name: B28 asp regular human insulin analogue

Molecular formula and molecular mass: C256H381N65079S6 and 5825.8 g/mole

Structural formula:

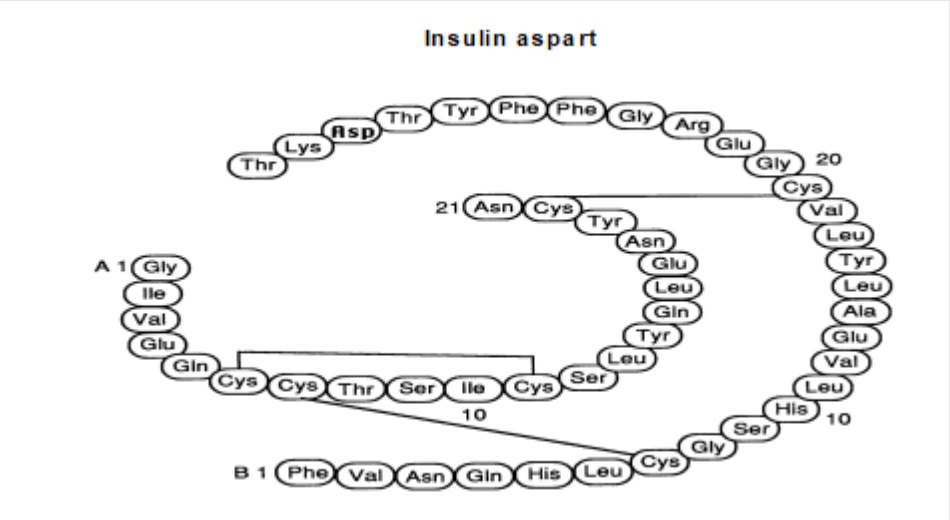


Figure 2 Structural formula of insulin aspart

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy of Fiasp® administered at mealtime or postmeal in adult patients with type 1 diabetes and used in combination with a once or twice daily administered basal insulin was evaluated in a randomized, treat-to-target, active-controlled trial.

The efficacy of Fiasp® administered at mealtime in adult patients with type 2 diabetes and used in combination with a once-daily administered basal insulin and metformin was evaluated in two randomized, treat-to-target, active-controlled trials.

The efficacy of Fiasp® administered by continuous subcutaneous insulin infusion (CSII) by external pump compared to NovoRapid® was evaluated in 472 adults with Type 1 diabetes.

The efficacy of Fiasp® was also evaluated in a 26-week randomized, active-controlled, treat-to-target trial in pediatric patients with type 1 diabetes ages 2 year and older.

Table 8 Summary of clinical trials in Type 1 and Type 2 diabetes

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age (range)	Gender
Type 1 Diabetes					
Study 3852 *Onset® 1*	Multicentre, multinational, randomized (1:1:1), 3-arm, partially double-blind, active controlled, treat-to-target, parallel group comparing mealtime Fiasp® and post-meal Fiasp® to NovoRapid®, in basal-bolus regimen with	Treatment arms: (1) Mealtime bolus treatment with Fiasp® SC (2) Post-meal bolus treatment with Fiasp® SC (3) Mealtime bolus	1143	44.4 years (18-83)	M:672 (58.8%) F:471 (41.2%)

	insulin detemir in T1DM adult patients.	treatment with NovoRapid® SC *All three arms were administered in combination with basal insulin detemir SC. Treatment duration: 26 weeks			
Study 3854 *Onset® 5*	Multicentre, multinational, randomized (1:1), double-blind, active controlled, treat-to-target, parallel group trial comparing CSII of Fiasp® vs. NovoRapid in T1DM adult patients.	Treatment arms: (1) Fiasp® SC (2) NovoRapid® SC Treatment duration: 4-week run-in and a 16-week treatment period	472	43.5 years (18-76)	M: 203 (43%) F: 269 (57%)
Study 4101 *Onset® 7*	Multicentre, multinational, randomized (1:1:1), active controlled, treat-to-target, 3-armed parallel-group trial in T1DM pediatric patients.	Treatment arms: (1) Blinded mealtime bolus treatment with Fiasp® SC (2) Blinded mealtime bolus treatment with NovoRapid® SC (3) Open-label postmeal bolus treatment with Fiasp® SC *All three arms were administered in combination with once-daily insulin degludec SC. Treatment duration: 26 weeks	777	11.7 years (2-17)	M: 419 (53.9%) F: 358 (46.1%)
Type 2 Diabetes					
Study 3853 *Onset® 2*	Multi-center, multi-national, randomized (1:1), double-blind, 2-arm, active-controlled, parallel-group, treat-to-target trial comparing mealtime Fiasp® and NovoRapid®,	Treatment arms: (1) Bolus treatment with Fiasp® SC (2) Bolus treatment with NovoRapid® SC	689	59.5 years (21-83)	M: 336 (48.8%) F: 353 (51.2%)

	both in basal-bolus regimen with insulin glargine + metformin in T2DM adult patients	*Both arms were administered in combination with basal insulin glargine SC, and metformin Treatment duration: 26 weeks			
Study 4049 *Onset® 3*	Multi-center, multi-national, randomized (1:1), open-label, parallel group trial evaluating efficacy and safety of mealtime Fiasp® in a basal-bolus regimen compared with basal insulin therapy, both in combination with metformin in T2DM patients	Treatment arms: (1) Bolus treatment with Fiasp® SC in combination with basal insulin detemir SC or insulin glargine SC or insulin NPH SC (2) Basal insulin therapy with insulin detemir SC or insulin glargine SC or insulin NPH SC *Both arms were administered in combination with metformin Treatment duration: 18 weeks	236	57.4 years (27-77)	M: 114 (48.3%)/ F: 122 (51.7%)

14.2 Study Results

Subcutaneous Daily Injections in Type 1 Diabetes - Adults
Study 3852: Fiasp® Administered in Basal-Bolus Regimen in Combination with Once or Twice Daily Insulin Detemir

A 26-week multinational, active controlled, treat-to-target trial was conducted to compare the efficacy and safety of mealtime Fiasp® (N=381) with mealtime NovoRapid® (N=380) and postmeal Fiasp® (N=382) with mealtime NovoRapid® in a basal-bolus regimen in combination with once or twice daily insulin detemir. Mealtime Fiasp® and NovoRapid® were injected 0-2 minutes before the meal, and postmeal Fiasp® was injected 20 minutes after the start of the meal. The premeal glycemic target during the treatment period was 4-6 mmol/L.

The mean age of the randomized subjects was 44.4 years and mean duration of diabetes was 19.9 years. 58.8% were male. 93.3% were Caucasian, 2.3% African American 6.9% were Hispanic. The mean BMI was 26.7 kg/m^2.

At Week 26, the difference in HbA_{1c} reduction from baseline between mealtime Fiasp® and NovoRapid® was -0.15% with 95% confidence interval [-0.23%; -0.07%] and met the pre-specified non-inferiority margin (0.4%). At week 26, the difference in HbA_{1c} reduction from baseline between post-meal Fiasp® and NovoRapid® was 0.04% with a 95% confidence interval of [-0.04%; 0.12%] and non-inferiority was confirmed. See Table 9.

In the mealtime Fiasp® treated group, the 2-hour PPG increment (standardized meal test) was 6.1 mmol/L at baseline and 5.9 mmol/L at end of trial. In the NovoRapid® treated group, the 2-hour PPG increment was 6.2 mmol/L at baseline and 6.6 mmol/L at end of trial. At Week 26, the estimated treatment difference in change from baseline in 2-hour PPG increment between mealtime Fiasp® and NovoRapid® was -0.67 mmol/L with 95% confidence interval [-1.29; -0.04].

Table 9 Subcutaneous Fiasp® Administration in Type 1 Diabetes (26 weeks; N=1143)

	Fiasp® mealtime + insulin detemir	**Fiasp® postmeal + insulin detemir**	**NovoRapid® mealtime + insulin detemir**
N	381	382	380
HbA_{1c} (%)			
Baseline, mean	7.6	7.6	7.6
End of trial, mean	7.3	7.5	7.4
Adjusted mean change from baseline	-0.32	-0.13	-0.17
Estimated treatment difference at Week 26 [95% CI] Fiasp® - NovoRapid®	-0.15 [-0.23; -0.07]	0.04 [-0.04;0.12]	
Proportion (%) achieving HbA_{1c} <7% at Week 26	33.3	23.3	28.2
Total bolus insulin dose (unit/kg/day)			
Baseline, median	0.33	0.35	0.36
End of trial, median	0.39	0.39	0.38
Total basal insulin dose (unit/kg/day)			
Baseline, median	0.41	0.43	0.43
End of trial, median	0.39	0.42	0.43
Body weight (kg)			
Baseline, mean	**78.6**	**80.5**	**80.2**
End of trial, mean	**79.2**	**81.2**	**80.7**
Adjusted mean change from baseline	**0.67**	**0.70**	**0.55**

N: number of subjects; CI: confidence interval.

Change from baseline in HbA_{1c} was analysed using a mixed-effect model for repeated measurements including changes from baseline at each visit. The model includes treatment, region and strata (combination of bolus adjusting method, basal treatment regimen and continuous glucose monitoring and frequently sampled meal test sub-group) as fixed effects, subject as random effect, baseline value as covariate and interaction between all fixed effects and visit, and between the covariate and visit. The model handles missing end of trial values by implicit imputation. Adjusted mean change from baseline in body weight was obtained by using a similar statistical model.

Subcutaneous Daily Injections in Type 2 Diabetes - Adults

Study 3853: Fiasp® Administered in Basal-Bolus Regimen in Combination with Basal Insulin and Metformin in Bolus Insulin Naïve Patients

A 26-week multicenter, multinational, randomized, double-blind, active controlled, treat-to-target, parallel group trial was conducted to compare the efficacy and safety of mealtime Fiasp® (N= 345) with mealtime NovoRapid® (N=344) in bolus-naïve subjects with type 2 diabetes. Both treatments were in combination with once-daily administered insulin glargine and metformin (≥1000 mg) in a basal-bolus regimen. Fiasp® or NovoRapid® was injected 0-2 minutes before the meal. The premeal glycemic target during the treatment period was 4-6 mmol/L. Patients enrolled in this study had to demonstrate inadequate glycemic control despite current treatment once daily basal insulin and metformin ≥1000 mg +/- other OAD, for at least 3 months prior to screening visit.

The mean age of the randomized subjects was 59.5 years and mean duration of diabetes was 12.7 years. 48.4% were male. 81% were Caucasian, 5.8% were African American and 6.4% were Hispanic. The mean BMI was 31.2 kg/m^2.

At Week 26, the difference in HbA_{1c} reduction from baseline between Fiasp® and NovoRapid® was -0.02% with 95% confidence interval [-0.15%; 0.10%] and met the pre-specified non-inferiority margin (0.4%). See Table 10.

In the Fiasp® treated group, the 2-hour PPG increment (standardized meal test) was 7.6 mmol/L at baseline and 4.6 mmol/L at end of trial. In the NovoRapid® treated group, the 2-hour PPG increment was 7.3 mmol/L at baseline and 4.9 mmol/L at end of trial. At Week 26, the estimated treatment difference in change from baseline in 2-hour PPG increment between Fiasp® and NovoRapid® was -0.36 mmol/L with 95% confidence interval [-0.81; 0.08].

Table 10 Subcutaneous Administration of Fiasp® in Type 2 Diabetes (26 weeks; N=689)

	Fiasp® + insulin glargine	**NovoRapid®+ insulin glargine**
N	345	344
HbA_{1c} (%)		
Baseline, mean	8.0	7.9
End of trial, mean	6.6	6.6
Adjusted mean change from baseline	-1.38	-1.36
Estimated treatment difference at Week 26 [95% CI] Fiasp® - NovoRapid®	-0.02[-0.15;0.10]	
Proportion (%) achieving HbA_{1c} <7% at Week 26	74.8	75.9
Total bolus insulin dose (unit/kg/day)		
Baseline, median	0.21	0.21
End of trial, median	0.49	0.51
Total basal insulin dose (unit/kg/day)		
Baseline, median	0.56	0.52
End of trial, median	0.53	0.48
Body weight (kg)		
Baseline, mean	89.0	88.3
End of trial, mean	91.6	90.8
Adjusted mean change from baseline	2.68	2.67
N: Number of subjects, CI: Confidence interval. Change from baseline in HbA1c was analysed using a mixed-effect model for repeated measurements including changes from baseline at each visit. The model includes treatment, region and continuous glucose monitoring strata as fixed effects, subject as random effect, baseline value as covariate and		

	Fiasp® + insulin glargine	NovoRapid®+ insulin glargine
interaction between all fixed effects and visit, and between the covariate and visit. The model handles missing end of trial values by implicit imputation. Adjusted mean change from baseline in body weight was obtained by using a similar statistical model.		

Study 4049: Fiasp® Administered in Basal-Bolus Regimen Compared to Basal Insulin in Combination with Metformin in Bolus Insulin Naïve Patients

An 18-week randomized, open-label, parallel, efficacy and safety trial was conducted to compare mealtime Fiasp® in full basal-bolus regimen (N=116) vs basal insulin therapy (N=120) in adult subjects with type 2 diabetes. The basal insulins used in both arms were insulin glargine, insulin detemir or NPH. All subjects were also on ≥1000 mg metformin treatment. Fiasp® was injected 0-2 minutes before the meal. The premeal glycemic target during the treatment period was 4-6 mmol/L. Patients enrolled in this study had to demonstrate inadequate glycemic control despite current treatment once daily basal insulin and metformin ≥1000 mg +/- other OAD, for at least 3 months prior to screening visit.

The mean age of the trial population was 57.4 years and mean duration of diabetes was 11.3 years. 48.3% were male. 69.9% were Caucasian, 3.8% African American37.3% were Hispanic. The mean BMI was 30.8 kg/m^2.

At baseline, HbA_{1c} was 7.9% in both treatment groups. At Week 18, reduction from baseline in HbA_{1c} was -1.16% in the Fiasp®+basal group, and -0.22% in the basal regimen only group. The difference in HbA1c reduction from baseline between the Fiasp® + basal group and the basal-only group was -0.94% with 95% confidence interval [-1.17;-0.72].

In the Fiasp® arm, 58.3% of patients experienced severe hypoglycemia (episode requiring assistance of another person) or BG confirmed hypoglycemia (episodes confirmed by plasma glucose <3.1 mmol/L), compared to 25% in the basal-regimen only group. The estimated mean body weight increased by 1.83 kg in the Fiasp®+basal group and by 0.17 kg in the basal group.

Median total bolus insulin dose increased from 0.23U/kg/day at baseline to 0.48U/kg/day at Week 18 in the Fiasp®+basal group, whereas the median total basal insulin remained the same over the duration of the trial (0.5U/kg/day in the Fiasp®+basal group and 0.6U/kg/day in the basal group.

Continuous Subcutaneous Insulin Infusion (CSII) in Type 1 Diabetes – Adults
Study 3854: Fiasp® in Continuous Subcutaneous Insulin Infusion (CSII) in Adults with Type 1 Diabetes Mellitus

The efficacy and safety of Fiasp® vs. NovoRapid® in CSII in adult subjects with T1DM (N=472) was evaluated in a randomized, multicentre, multinational, active controlled, treat-to-target, parallel group trial with a 4-week run-in and a 16-week treatment period.

The mean age of the randomized subjects was 43 years and the mean duration of diabetes was 24 years. 43% were male. 89% were Caucasian, 1% were Black or African American, 1% were Asian, and 3% were Hispanic. The mean BMI was 26.3 kg/m^2.

At Week 16, the difference in change in HbA_{1c} from baseline between Fiasp® and NovoRapid® was 0.09% with 95% confidence interval [0.01%; 0.17%] and met the pre-specified non-inferiority margin (0.4%). See Table 11.

The insulin doses were similar for the two treatment arms at the end of the trial.

In the Fiasp® treated group, the 1-hour PPG increment (standardized meal test) was 4.67 mmol/L at baseline and 3.74 mmol/L at the end of trial. In the NovoRapid® treated group, the 1-hour PPG increment was 4.62 mmol/L at baseline and 4.70 mmol/L at the end of trial.

Table 11 Continuous Subcutaneous Insulin Infusion of Fiasp® in Type 1 Diabetes – Adults 16 weeks; N=472)

	Fiasp®	**NovoRapid®**
N	236	236
HbA_{1c} (%)		
Baseline, mean	7.49	7.49
End of trial, mean	7.44	7.35
Adjusted mean change from baseline	-0.05	-0.15
Estimated treatment difference at Week 16 [95% CI] Fiasp® - NovoRapid®	0.09 [0.01;0.17]	
Proportion (%) achieving HbA_{1c} <7% at Week 16 without severe hypoglycaemia	18.6%	22.5%
Proportion (%) achieving HbA_{1c} <7% at Week 16	20.3%	23.3%

Subcutaneous Daily Injections in Type 1 Diabetes Pediatric Patients 2 Years of Age and Older

Study 4101: Fiasp® added to insulin degludec in pediatric patients 2 years of age and older with Type 1 DM.

The efficacy of Fiasp® in pediatric patients was evaluated in a 26-week, randomised, multicentre, multinational, active controlled, treat-to-target, 3-armed parallel-group trial in 777 pediatric patients with type 1 diabetes. Patients were randomized to either blinded mealtime Fiasp® (N=260), blinded mealtime NovoRapid® (N=258), or open-label postmeal Fiasp® (N=259), all in combination with once daily insulin degludec. Mealtime Fiasp® or NovoRapid® was injected 0-2 minutes before the meal, and postmeal Fiasp® was injected 20 minutes after the start of the meal.

The mean age of the subjects at baseline was 11.7 years and the mean duration of diabetes was 4.4 years. 54% were male, 81% were Caucasian, 16% were Asian and 2% were Black or African American. The Mean BMI was 19.7 kg/m^2.

At Week 26, the difference in change in HbA_{1c} from baseline between mealtime Fiasp® and mealtime NovoRapid® was -0.17% with 95% confidence interval [-0.30%; -0.03%] and met the pre-specified non-inferiority margin (0.4%). See Table 12 .

The estimated rate ratio for severe or BG confirmed hypoglycemic episodes was 1.11 [0.90; 1.37]$_{95\%CI}$ for both mealtime Fiasp® and post-meal Fiasp® compared to mealtime NovoRapid®. The estimated rate ratio for nocturnal severe or BG confirmed hypoglycemic episodes for mealtime Fiasp® compared to NovoRapid® was 1.29 [0.93; 1.79]$_{95\%CI}$. For Fiasp® post-meal, compared to NovoRapid® a higher rate of nocturnal severe or BG confirmed hypoglycemic episodes was reported with an estimated rate ratio of 1.50 [1.09; 2.08]$_{95\%CI}$.

Table 12 Subcutaneous Fiasp® Administration in Type 1 Diabetes - Pediatric (26 weeks; N=777)

	Mealtime Fiasp® **+ insulin degludec**	**Postmeal Fiasp®** **+ insulin degludec**	**Mealtime NovoRapid®** **+ insulin degludec**
Number of subjects randomized (N)	**260**	**259**	**258**
HbA_{1c} (%)			
Baseline (mean)	7.57	7.58	7.53
End of trial (mean)	7.63	7.91	7.76
Adjusted mean change from baseline	0.06	0.35	0.22
Estimated treatment difference vs. mealtime NovoRapid® [95% CI]*	-0.17 [-0.30; -0.03]	0.13 [-0.01; 0.26]	

Baseline is based on the mean of the observed last available values prior to randomization.
* tested for non-inferiority.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of Fiasp®.

In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with insulin aspart at 10, 50, and 200 units/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 units/kg/day, based on units/body surface area, respectively). At a dose of 200 units/kg/day, insulin aspart increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for insulin aspart was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. Insulin aspart was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and in ex vivo UDS test in rat liver hepatocytes. In fertility studies in male and female rats, at subcutaneous doses up to 200 units/kg/day (approximately 32 times the human subcutaneous dose, based on units/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

17 SUPPORTING PRODUCT MONOGRAPHS

NovoRapid® (Solution, 100 U/mL, Subcutaneous use), submission control No: 211441, Product Monograph, Novo Nordisk Canada Inc. (APR, 06, 2018)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

FIASP®

vial/Penfill®/FlexTouch®

insulin aspart injection

Solution, 100 U/mL, subcutaneous use

Read this carefully before you start taking **Fiasp®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Fiasp®**.

Serious Warnings and Precautions

- Low blood sugar is the most common adverse effect of insulin products, including Fiasp®.
- If low blood sugar or high blood sugar reactions are not treated, they can cause loss of consciousness, coma or even death.
- Blood sugar levels should be monitored for all patients with diabetes.
- Fiasp® should be injected up to 2 minutes before the start of the meal. When necessary, Fiasp® may be administered up to 20 minutes after starting the meal. (See *'How to take Fiasp®?')*
- Accidental mix-up between Fiasp® and other insulin products have been reported. Always carefully check the insulin label before each injection to avoid mix-ups between insulin products.
- DO NOT dilute or mix Fiasp® with any other insulin products or solutions, except when given into your vein under medical supervision.
- Fiasp® should generally be used in a regimen with intermediate- or long-acting insulin (plus metformin for type 2 diabetes as recommended) or with insulin infusion pump therapy to maintain blood sugar levels.
- Only use Fiasp® if the solution looks water-clear and colourless.

What is Fiasp® used for?

- The treatment of adults and children 2 years and above with diabetes mellitus who require insulin for the control of high blood sugar.
- The treatment of type 2 diabetes patients generally used in combination with an intermediate- or long-acting insulin (plus metformin) for the control of high blood sugar.

How does Fiasp® work?

Fiasp® is a fast-acting mealtime insulin aspart formulation used to treat diabetes. Fiasp® will start to lower your blood sugar within 20 minutes after starting a meal. Due to this short action Fiasp® should normally be taken in combination with intermediate- or long-acting insulin preparation (plus metformin for type 2 diabetes as recommended).

What are the ingredients in Fiasp®?

Medicinal ingredients: The active ingredient in Fiasp® is insulin aspart.
Non-medicinal ingredients: Arginine (as L-arginine HCl), disodium-phosphate dihydrate, glycerol, metacresol, niacinamide (vitamin B_3), phenol, water for injections, and zinc (as zinc acetate). Hydrochloric acid and/or sodium hydroxide may be added for pH adjustment.

Fiasp® comes in the following dosage forms:
• Fiasp® 10 mL vial (1,000 units per 10 mL); Pack size: 1 vial of 10 mL
• Fiasp® Penfill® 3 mL cartridge (designed for use with Novo Nordisk Insulin Delivery Devices) (300 units per 3 mL); Pack size: 5 cartridges of 3 mL
• Fiasp® FlexTouch® 3 mL prefilled pen (300 units per 3 mL); Pack size: 5 pre-filled pens of 3 mL

Fiasp® 10 mL vial can be used for continuous infusion in a pump system.

Fiasp® is presented as a water-clear, colourless and aqueous solution for injection. Each mL contains 100 units of insulin aspart.

Fiasp® FlexTouch® and Fiasp® Penfill® in a Novo Nordisk Insulin Delivery Device is designed for use with NovoFine®, NovoFine® Plus and/or NovoTwist® needles as part of The All-In-One System®. Novo Nordisk cannot be held responsible for malfunctions occurring as a consequence of using Fiasp® with products that do not meet the same specifications or quality standards as NovoFine®, NovoFine® Plus and/or NovoTwist® needles.

Do not use Fiasp® if:
- You feel a low blood sugar coming on. (see *'What are possible side effects from using Fiasp®?'* for more about low blood sugar).
- You are allergic (hypersensitive) to insulin aspart, metacresol or any of the other ingredients in this insulin. Look out for the signs of an allergic reaction. (see *'What are possible side effects from using Fiasp®?')*.
- If the protective cap is loose or missing. Each vial has a protective, tamper proof plastic cap. If the cap is not in perfect condition when you get the vial, return the vial to your supplier.
- If the Penfill® cartridge or Novo Nordisk Insulin Delivery Device containing the cartridge is dropped, damaged or crushed; there is a risk of leakage of insulin.
- The FlexTouch® is dropped, damaged or crushed; there is a risk of leakage of insulin.
- The insulin has not been stored correctly or if it has been frozen. (see *'Storage')*
- The insulin does not appear water-clear and colourless.
- Taking thiazolidinediones (class of oral antidiabetic drugs) together with insulin may increase risk of oedema and heart failure. Inform your doctor as soon as possible if you experience localised swelling (oedema) or signs of heart failure such as unusual shortness of breath.

Do not refill a Fiasp® Penfill® cartridge.

If you are treated with Fiasp® Penfill® and another insulin in Penfill® cartridge, you should use two Novo Nordisk Insulin Delivery Devices, one for each type of insulin.

As a precautionary measure:
- Always carry a spare insulin delivery device with a Penfill® cartridge or FlexTouch® and new needles with you, in case of loss or damage.
- Always carry something to show you have diabetes.
- Always carry products containing sugar with you. See the section on '*Causes of low blood sugar (hypoglycemia): What to do if you get any of these signs*'.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Fiasp®. Talk about any health conditions or problems you may have, including if you:

- Have trouble with your adrenal, pituitary or thyroid glands, your doctor may decide to alter your insulin dose.
- Have an infection, fever or have had an operation you may need more insulin than usual.
- Suffer from diarrhea, vomiting or eat less than usual you may need less insulin than usual.
- Exercise more than usual or if you want to change your usual diet.
- Are ill: continue taking your insulin. Your need for insulin may change.
- Go abroad: travelling over time zones may affect your insulin needs and the timing of your injections. Consult your doctor if you are planning such travel.
- Are pregnant, or planning a pregnancy or are breastfeeding please contact your doctor for advice.
- Drive or use tools or machines: watch for signs of a hypoglycemia. Your ability to concentrate or to react will be less during a hypoglycemic reaction. Please keep this in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypoglycemic reaction coming on.

Other warnings you should know about:

- The onset of effect for Fiasp® is twice as fast when compared to NovoRapid®. Therefore if low blood sugar occurs, you may experience it earlier after an injection.
- Hypokalemia (low potassium) is a possible side effect with all insulins. You might be more at risk if you are on potassium lowering drugs or losing potassium (e.g. diarrhea).
- Eye disorder - Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disorder.
- Pain due to nerve damage - If your blood sugar level improves very fast, you may get nerve related pain, this is usually temporary.
- Swelling around your joints - When you first start using your medicine, your body may keep more water than it should. This causes swelling around your ankles and other joints. This is usually only short-lasting.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Fiasp®:

Some medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Tell your doctor, Diabetes Nurse Educator or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

If you take any of the medicines below, your blood sugar level may fall (hypoglycemia)

- Other medicines for the treatment of diabetes
- Medicines used to treat high blood pressure and/or heart problems, such as: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blocking (ARB) agents, disopyramide

- Fibrates (medicine used for lowering high levels of blood fats)
- Monoamine oxidase inhibitors (MAOI) (medicines used to treat depression)
- Medicines used to relieve pain and lower fever, such as pentoxifylline, propxyphene and salicylates
- Sulfonamide antibiotics (medicines used to treat infections)
- Somatostatin analogs, such as octreotide
- Fluoxetine

If you take any of the medicines below, your blood sugar level may rise (hyperglycemia)

- Atypical antipsychotics (e.g., olanzapine and clozapine)
- Hormones, such as: estrogens and/or progesterone (alone or as contraceptive pills), somatropin, thyroid hormones, glucagon.
- Corticosteroids (used to treat inflammation)
- Danazol (medicine acting on ovulation)
- Protease inhibitors (used to treat HIV infection)
- Diuretics (also called water pills), used to treat high blood pressure or fluid retention
- Isoniazid (used to treat tuberculosis)
- Some medicines used to treat asthma, such as albuterol, epinephrine, terbutaline
- Niacin and phenothiazines

If you take any of the medicines below, your blood sugar level may rise or fall

- High blood pressure medicines, such as: beta-blockers or clonidine
- Some medicines used to treat mental health problems, such as: lithium salts.
- Octreotide and lanreotide (used to treat a rare condition involving too much growth hormone (acromegaly))
- Alcohol (including wine and beer)
- A medicine used to treat some parasitic infections, called pentamidine. This may cause too low blood sugar which is sometimes followed by too high blood sugar.

Some medicines may make it harder to recognize the warning signs of your blood sugar being too low (hypoglycemia). Such medicines include: beta-blockers medicines, clonidine, guanethidine, or reserpine.

Before using Fiasp®

- Check the label to make sure you have the right type of insulin.
- Remove the protective cap.
- Always check the Penfill® cartridge, including the rubber stopper (plunger). Don't use it if any damage is seen or if there is a gap between the rubber stopper and the white barcode label. Take it back to your supplier or call Novo Nordisk Canada at 1-800-465-4334 for assistance. See your Novo Nordisk Insulin Delivery Device manual for further instructions.
- Always use a new needle for each injection to prevent contamination.
- Do not share your Fiasp® Penfill® in a Novo Nordisk Insulin Delivery Device/FlexTouch® with another person, even if the needle is changed. Do not reuse or share needles with another person. You may give another person an infection or get an infection from them.
- The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may

not work very well if you inject into a lumpy, shrunken or thickened area (see 'How to use Fiasp®'). Tell your healthcare professional if you notice any skin changes at the injection site. Tell your healthcare professional if you are currently injecting into these affected areas before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your healthcare professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

How to take Fiasp®:
Fiasp® is for injection under the skin (subcutaneously) or for continuous infusion in pumps. Administration in a pump will require a comprehensive instruction by your healthcare professional. Do not inject into a vein or muscle.

Always vary the site you inject within the same region, to avoid lumps (see *'What are possible side effects from using Fiasp®?'*). The best places to give yourself an injection are: the front of your thighs; the front of your waist (abdomen); or the upper arm. Your insulin will work more quickly if you inject around the waist.

You should always measure your blood glucose regularly.

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. Do not change your insulin unless your doctor tells you to. Follow their advice carefully. This leaflet is a general guide only.

If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Due to the faster onset of action, Fiasp® should be injected up to 2 minutes before the start of a meal. When necessary, Fiasp® may be administered up to 20 minutes after starting a meal.

How to inject this insulin using a vial
- Draw into the syringe the same amount of air as the dose of insulin you are going to inject. Inject the air into the vial.
- Turn the vial and syringe upside down and draw the correct insulin dose into the syringe. Pull the needle out of the vial. Then expel the air from the syringe and check that the dose is correct.
- Inject the insulin under the skin. Use the injection technique advised by your doctor or Diabetes Nurse Educator.
- Discard needle after each injection.

For use in an insulin infusion pump system using a vial:
Follow the instructions and recommendations from your doctor regarding the use of Fiasp® in a pump. Before using Fiasp® in the pump system, you must have received a comprehensive instruction in the use and information about any actions to be taken in case of illness, too high or too low blood sugar or failure of the pump system. If you use Fiasp® from a vial in an infusion pump system it can be used for a maximum of 6 days.

Filling the pump using a vial:
- Fiasp® should never be diluted or mixed with any other insulin.

- Before inserting the needle, use soap and water to clean your hands and the skin where the needle is inserted to avoid any infection at the infusion site.
- When you fill a new reservoir, do not leave large air bubbles in either the syringe or the tubing.
- Changing of the infusion set (tubing and needle) must be done according to the instructions in the product information supplied with the infusion set.

To get the benefit of insulin infusion, and to detect possible malfunction of the insulin infusion pump, it is recommended that you measure your blood sugar level regularly.

What to do if the pump system fails
You should always have an alternative delivery method for your insulin available for injection under the skin (for example, a pen injector or syringes) in case the pump system fails.

How to inject this insulin using a Penfill® cartridge:
- Please read the manual that comes with your insulin delivery device.
- Inject the insulin under the skin. Use the injection technique advised by your doctor or Diabetes Nurse Educator and described in your Novo Nordisk Insulin Delivery Device Manual. Keep the needle under your skin for at least six seconds. Keep the push button fully depressed until the needle has been withdrawn. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir.
- After each injection discard the needle.

How to inject this insulin FlexTouch®:
Detailed instructions for use are provided on the other side of this leaflet.

Usual dose:

When to use Fiasp®:
Fiasp® is a mealtime insulin. Fiasp® should be injected up to 2 minutes before the start of a meal. When necessary, Fiasp® may be administered up to 20 minutes after starting a meal. A maximum effect occurs between 1 and 3 hours after the injection and the effect lasts for 3-5 hours.

Fiasp® dose
Dose for type 1 and type 2 diabetes
Your doctor will decide together with you:
- How much Fiasp® you will need at each meal
- When to check your blood sugar level and if you need a higher or lower dose.

If you want to change your usual diet, first check with your doctor, Diabetes Nurse Educator or pharmacist as a change in diet may alter your need for insulin.

When using other medicines, ask your doctor or Diabetes Nurse Educator if your treatment needs to be adjusted.

Dose adjustment for type 2 diabetes
The dose each day for Fiasp® should be based on your blood sugar level at mealtimes and bedtime from the previous day.

- Before breakfast - dose should be adjusted according to the blood sugar level before lunch the previous day.
- Before lunch - dose should be adjusted according to the blood sugar level before dinner the previous day.
- Before dinner - dose should be adjusted according to the bedtime blood sugar level the previous day.

Dose adjustment	
Mealtime or bedtime plasma glucose	**Dose adjustment**
less than 4.0 mmol/L	Reduce dose by 1 unit
4.0 - 6.0 mmol/L	no adjustment
more than 6.0 mmol/L	Increase dose by 1 unit

Use in elderly patients (65 years or older)
Fiasp® can be used in geriatric patients but if you are geriatric you may need to check your blood sugar level more often. Talk to your doctor about changes in your dose.

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

Overdose:

Causes of low blood sugar (hypoglycemia):
You get a hypoglycemia if your blood sugar gets too low.
This might happen:
- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual
- If you drink alcohol

The warning signs of a hypoglycemia may come on suddenly and can include: cold sweat; cool pale skin; headache; slurred speech; fast heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; and difficulty concentrating.

What to do if you get any of these signs:
- Eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest. Don't take any insulin if you feel a hypoglycemia coming on.
- Measure your blood sugar if possible and rest. You may need to measure your blood sugar more than once.
- 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.

If severe hypoglycemia is not treated, it can cause brain damage (temporary or permanent) and even death.

If you have a hypoglycemia that makes you pass out, or if you get a lot of hypoglycemias, talk

to your doctor. The amount or timing of your insulin dose, the amount of food you eat or the amount of exercise you do, may need to be adjusted.

What others need to do if you pass out:
Tell your relatives, friends and close colleagues that if you pass out (become unconscious); they must turn you on your side and get medical help right away. They must not give you anything to eat or drink as it could choke you.

Using glucagon
You may recover more quickly from unconsciousness with an injection of the hormone glucagon given by someone who knows how to use it. If you are given glucagon you will need to eat glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or hospital emergency after an injection of glucagon: you need to find the reason for your hypoglycemia in order to avoid getting more.

If you think you, or a person you are caring for, have taken too much Fiasp®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Causes of high blood sugar (hyperglycemia):

You get a hyperglycemia if your blood sugar gets too high.
This might happen:

- If you forget to take or stop taking insulin
- If you keep taking less insulin than you need
- If you eat more than usual
- If you exercise less than usual
- If you drink alcohol
- If you get an infection or fever

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed dry skin; a dry mouth and a fruity (acetone) smelling breath.

These may be signs of a very serious condition called diabetic ketoacidosis (a condition with too much acid in the blood). If you don't treat it, this could lead to diabetic coma and death.

What to do if you get any of these signs: test your blood sugar level; test your urine for ketones if you can; then seek medical advice right away.

Causes of low potassium (hypokalemia)

If you take too much insulin, particularly when given intravenously, it might cause hypokalemia (low potassium). Hypokalemia must be corrected appropriately.

Missed Dose:

If you have missed a dose of Fiasp® or if you have not injected enough insulin, your blood sugar level may become too high (hyperglycemia). Check your blood sugar frequently. For information on the treatment of hyperglycemia, see *'Causes of high blood sugar*

(hyperglycemia)' above.

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

What are possible side effects from using Fiasp®?

These are not all the possible side effects you may feel when taking Fiasp®. If you experience any side effects not listed here, contact your healthcare professional.

The following side effects may be observed while taking Fiasp®:

- Very common (more than 1 out of 10 patients)
  - Low Blood Sugar (See section '*Causes of low blood sugar (hypoglycemia)*' above)
- Common (less than 1 out of 10 patients)
  - Reaction at administrations site
  - Skin reactions
- Uncommon
  - Changes under the skin where you use the injection (Lipodystrophy)
  - Allergic reactions
- Frequency not known
  - Lumps under the skin (Cutaneous Amyloidosis)

Reaction at administration site: Local reactions at the place you inject/infuse yourself may occur. The signs may include: rash, redness, inflammation, bruising and itching. The reactions usually disappear after a few days.

Skin reactions: Signs of allergy on the skin such as eczema, rash, itching, hives and dermatitis may occur.

Changes under the skin where you use the injection (lipodystrophy): Fatty tissue under the skin may shrink (lipoatrophy) or get thicker (lipohypertrophy). Changing where you inject each time may reduce the risk of developing these skin changes. If you notice these skin changes, tell your doctor or nurse. If you keep injecting in the same place, these reactions can become more severe and affect the amount of medicine your body gets.

Allergic reaction: If you have a serious allergic reaction to the insulin or any of the ingredients in Fiasp®, stop using Fiasp® and see a doctor straight away. The signs of a serious allergic reaction may include:

- Local reactions (e.g., rash, redness, and itching) spread to other parts of your body
- You suddenly feel unwell with sweating
- You start being sick (vomiting)
- You experience difficulty in breathing
- You experience rapid heart beat or feeling dizzy.

Cutaneous Amyloidosis: Lumps under the skin may also be caused by build-up of protein called amyloid (cutaneous amyloidosis). The insulin 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.

Serious side effects and what to do about them

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Hypoglycemia	√		√
COMMON Reaction at administration site		√	
Skin reactions		√	
RARE Changes under the skin where you use the injection (lipodystrophy)		√	
Allergic reaction			√
UNKNOWN Cutaneous Amyloidosis: lumps under skin		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

Before first use:
[FlexTouch®] Store in the refrigerator (2°C to 8°C). Keep away from the freezing element. Do not freeze. Keep the cap on the pen in order to protect from light.
[Penfill®] Store in the refrigerator (2°C to 8°C). Keep away from the freezing element. Do not freeze. Keep the cartridge in the carton in order to protect from light.
[Vial] Store in the refrigerator (2°C to 8°C). Keep away from the freezing element. Do not freeze. Keep the vial in the carton in order to protect from light.

After first opening or if carried as a spare:

[FlexTouch®] You can carry your Fiasp® pre-filled pen (FlexTouch®) with you and keep it at room temperature (not above 30°C) or in a refrigerator (2°C to 8°C) for up to 4 weeks. Always keep the cap on the pen when you are not using it in order to protect from light.
[Penfill®] Do not refrigerate. You can carry your cartridge (Penfill®) with you and keep it at room temperature (not above 30°C) for up to 4 weeks. Always keep the cartridge in the carton in order to protect from light.
[FlexTouch®][Penfill®] Throw away the needle after each injection.
[Vial] You can carry your Fiasp® vial with you and keep it at room temperature (not above 30°C) or in a refrigerator (2°C to 8°C) for up to 4 weeks (including the time it has been stored inside of a pump reservoir). Always keep the vial in the carton in order to protect from light.

When used in an insulin infusion pump system:
Fiasp® inside of the pump reservoir should be replaced:

- At least every 6 days, or according to the instructions in the product information supplied with the infusion set, whichever is shorter, or
- After being exposed to temperatures above 37°C

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.

If you want more information about Fiasp®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.novonordisk.ca, or by calling 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

Novo Nordisk Canada Inc.

Last Revised JUL 23, 2021

Instructions on how to use Fiasp® FlexTouch®

Please read these instructions carefully before using your FlexTouch® pre-filled pen. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

Do not use the pen without proper training from your doctor or nurse.
Start by checking your pen to **make sure that it contains Fiasp® 100 units/mL**, then look at the illustrations below to get to know the different parts of your pen and needle.

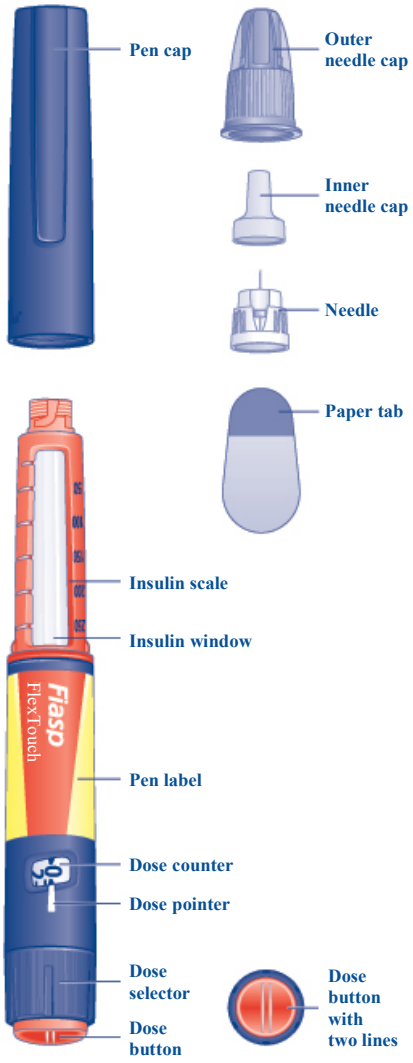
If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight that is trained to use the FlexTouch® pre-filled pen.

Your pen is a pre-filled dial-a-dose insulin pen containing 300 units of insulin. You can select a **maximum of 80 units per dose, in steps of 1 unit**. Your pen is designed to be used with NovoTwist®, NovoFine® or NovoFine® Plus single-use, disposable needles up to a length of 8 mm. Needles are not included in the pack.

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

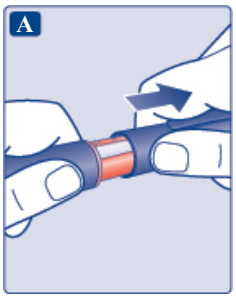
Fiasp® Pre-filled pen and needle (example) (FlexTouch®)

Fiasp pre-filled pen and needle (example) (FlexTouch)

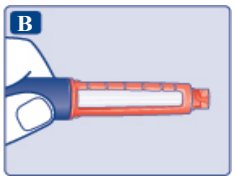


1 Prepare your pen with a new needle

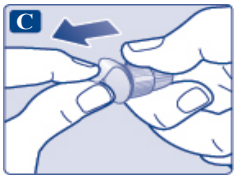
- **Check the name and strength on the label** of your pen, to make sure that it contains Fiasp® 100 units/mL. This is especially important if you take more than one type of insulin. If you take a wrong type of insulin, your blood sugar level may get too high or too low.
- **Pull off the pen cap.**



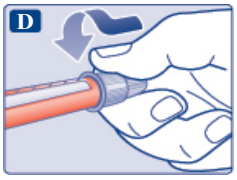
- **Check that the insulin in your pen is water-clear** and colourless.
  Look through the insulin window. If the insulin looks cloudy, do not use the pen.



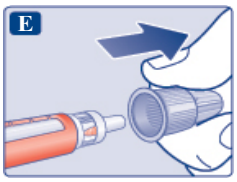
- **Take a new needle** and tear off the paper tab.



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



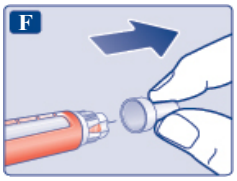
- **Pull off the outer needle cap and keep it for later.** You will need it after the injection, to safely remove the needle from the pen.



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

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

Do not attach a new needle to your pen until you are ready to take your injection.

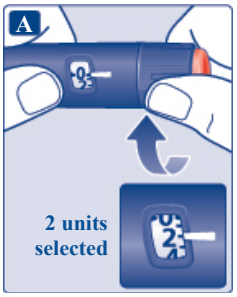


Always use a new needle for each injection.
This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

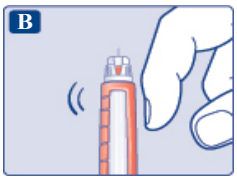
Never use a bent or damaged needle.

2 Check the insulin flow

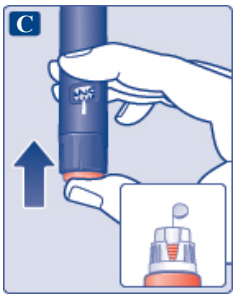
- **Always check the insulin flow before you start.**
  This helps you to ensure that you get your full insulin dose.
- Turn the dose selector to **select 2 units. Make sure the dose counter shows 2.**



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



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



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

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

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

⚠ **Always make sure that a drop appears** at the needle tip before you inject. This makes sure that the insulin flows.
If no drop appears, you will **not** inject any insulin, even though the dose counter may move. This may indicate a blocked or damaged needle.

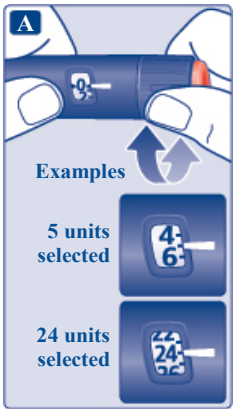
⚠ **Always check the flow before you inject.** If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

3 Select your dose

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

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

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



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

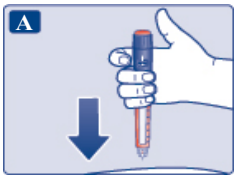
You can select up to 80 units per dose. When your pen contains less than 80 units, the dose counter stops at the number of units left.

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

⚠ **Always use the dose counter and the dose pointer to see how many units you have selected before injecting the insulin.**
Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low.
Do not use the insulin scale, it only shows approximately how much insulin is left in your pen.

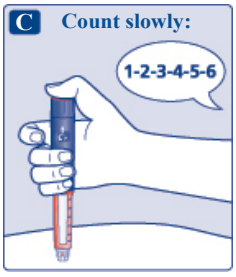
4 Inject your dose

- **Insert the needle into your skin** as your doctor or nurse has shown you.
- **Make sure you can see the dose counter.**
  Do not touch the dose counter with your fingers. This could interrupt the injection.

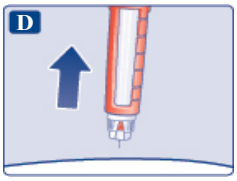


- **Press and hold down the dose button until the dose counter shows 0.**
  The 0 must line up with the dose pointer. You may then hear or feel a click.

- **Keep the needle in your skin after** the dose counter has returned to 0 and **count slowly to 6.**
- If the needle is removed earlier, you may see a stream of insulin coming from the needle tip. If so, the full dose will not be delivered, and you should increase the frequency of checking your blood sugar level.



- **Remove the needle from your skin.** If blood appears at the injection site, press lightly. Do not rub the area.



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

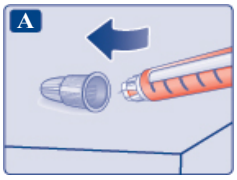
⚠ **Always watch the dose counter to know how many units you inject.** Hold the dose button down until the dose counter shows 0. If the dose counter does not return to 0, the full dose has not been delivered, which may lead to too high blood sugar level.

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** medicine - even though the dose counter has moved from the original dose that you have set.

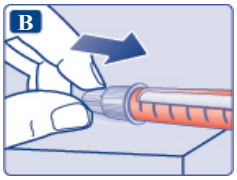
How to handle a blocked needle?
Remove the needle as described in section 5 and repeat all steps starting with section 1: Prepare your pen with a new needle. Make sure you select the full dose you need.

Never touch the dose counter when you inject.
This can interrupt the injection.

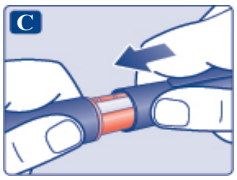
5 After your injection
- **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer cap.



- Once the needle is covered, **carefully push the outer needle cap completely on.**
- **Unscrew the needle** and dispose of it carefully, as instructed by your doctor, nurse, pharmacist or local authorities.



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



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

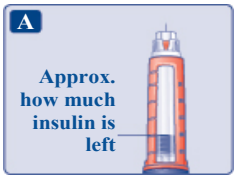
When the pen is empty, throw it away **without** a needle on as instructed by your doctor, nurse, pharmacist or local authorities.

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

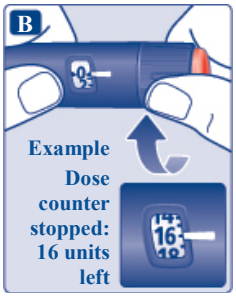
⚠ **Always remove the needle from your pen after each injection** and store your pen without the needle attached**.** This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

6 How much insulin is left?

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



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



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

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

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

Further important information

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

Caring for your pen

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

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