

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

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of the solution contains 100 units of insulin aspart* (equivalent to 3.5 mg).

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

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

Fiasp 100 units/mL solution for injection in cartridge

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

Fiasp 100 units/mL solution for injection in vial

One vial contains 1,000 units of insulin aspart in 10 mL solution.

*Insulin aspart is produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

Solution for injection (FlexTouch).

Fiasp 100 units/mL solution for injection in cartridge

Solution for injection (Penfill).

Fiasp 100 units/mL solution for injection in vial

Solution for injection.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

4.2 Posology and method of administration

Posology

Fiasp is a mealtime insulin for subcutaneous administration up to 2 minutes before the start of the meal, with the option to administer up to 20 minutes after starting the meal (see section 5.1).

Dosing with Fiasp is individual and determined in accordance with the needs of the patient. Fiasp given by subcutaneous injection should be used in combination with intermediate-acting or long-acting insulin given at least once a day. In a basal-bolus treatment regimen approximately 50% of this requirement may be provided by Fiasp and the remaining by intermediate-acting or long-acting insulin.

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.

Blood glucose monitoring and insulin dose adjustment are recommended to achieve optimal glycaemic control.

Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness. Blood glucose levels should be monitored adequately under these conditions.

The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

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.

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.

The early onset of action must be considered when prescribing Fiasp (see section 5.1).

Initiation

Patients with type 1 diabetes mellitus

The recommended starting dose in insulin naïve patients with type 1 diabetes is approximately 50% of the total daily insulin dose and should be divided between the meals based on the size and composition of the meals. The remainder of the total daily insulin dose should be administered as intermediate-acting 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.

Patients with type 2 diabetes mellitus

Suggested initial dose is 4 units at one or more meals. Number of injections and subsequent titration will depend on the individual glycaemic target and the size and composition of the meals.

Dose adjustment may be considered daily based on self-measured plasma glucose (SMPG) on the previous day(s) according to Table 1.

- Pre-breakfast dose should be adjusted according to the pre-lunch SMPG the previous day
- Pre-lunch dose should be adjusted according to the pre-dinner SMPG the previous day
- Pre-dinner dose should be adjusted according to the bedtime SMPG the previous day

Table 1 Dose adjustment

SMPG (see above)		Dose adjustment
mmol/L	mg/dL	Unit
<4.0	<71	-1
4.0–6.0	71–108	No adjustment
>6.0	>108	+1

Special populations

Elderly patients (≥ 65 years old)

The safety and efficacy of Fiasp have been established in elderly patients aged 65 to 75 years. Close glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis (see section 5.1 and 5.2). The therapeutic experience in patients ≥ 75 years of age is limited.

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 (see section 5.2).

Paediatric population

Fiasp can be used in adolescents and children from the age of 1 year (see section 5.1). There is no clinical experience with the use of Fiasp in children below the age of 2 year.

Fiasp is recommended to be administered prior to the meal (0-2 minutes), with the flexibility to administer up to 20 minutes after starting the meal in situations, when there is uncertainty about the meal intake.

Transfer from other insulin medicinal products

Close glucose monitoring is recommended during the transfer from other mealtime insulins and in the initial weeks thereafter. Converting from another mealtime insulin can be done on a unit-to-unit basis. Transferring a patient from another type, brand or manufacturer of insulin to Fiasp must be done under strict medical supervision and may result in the need for a change in dosage.

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

Method of administration

Subcutaneous injection

Fiasp is recommended to be administered subcutaneously in the abdominal wall or the upper arm (see section 5.2). Injection sites should be rotated within the same region in order to reduce the risk of lipodystrophy.

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

Administration with a pre-filled pen (FlexTouch)

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

FlexTouch is colour-coded and accompanied by a package leaflet with detailed instructions for use to be followed.

The pre-filled pen is only suitable for subcutaneous injections. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used.

Fiasp 100 units/mL solution for injection in cartridge

Administration with a reusable insulin pen

The cartridge (Penfill) is designed to be used with Novo Nordisk reusable insulin pens and NovoFine Plus, NovoFine or NovoTwist injection needles for subcutaneous injection only.

If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used.

Fiasp 100 units/mL solution for injection in vial

Administration with a syringe

The vial is to be used with insulin syringes with the corresponding unit scale (U-100 or 100 U/mL).

Continuous subcutaneous insulin infusion (CSII)

Fiasp can be used for CSII in pumps suitable for insulin infusion and will cover both the bolus insulin requirement (approximately 50%) and basal insulin. It can be administered in accordance with the instructions provided by the pump manufacturer, preferably in the abdomen. Infusion site should be rotated within the same region to reduce the risk of lipodystrophy. When used with an insulin infusion pump, it should not be diluted or mixed with any other insulin medicinal products.

Patients using CSII should be instructed in the use of the pump and use the correct reservoir and tubing for pump (see section 6.6). The infusion set (tubing and cannula) should be changed in accordance with the instructions in the product information supplied with the infusion set.

Patients administering Fiasp by CSII must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure.

Intravenous use

If necessary, Fiasp can be administered intravenously by health care professionals.

For intravenous use, it 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 the infusion fluids such as sodium chloride 9 mg/mL (0.9%) solution or 5% glucose solution.

Monitoring of blood glucose is necessary during insulin infusion. Care should be taken to ensure that the insulin is injected into the infusion bag and not simply the entry port.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypoglycaemia

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

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

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

The timing of hypoglycaemia usually reflects the time-action profile of the administered insulin formulation. Hypoglycaemia may occur earlier after an injection/infusion when compared to other mealtime insulins due to the earlier onset of action of Fiasp (see section 5.1).

Since Fiasp should be administered up to 2 minutes before the start of the meal with the option to administer up to 20 minutes after starting the meal, the time to onset of action must be taken into account when prescribing to patients with concomitant diseases or treatment where a delayed absorption of food might be expected.

Paediatric population

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 hypoglycaemia.

Hyperglycaemia

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

Continuous subcutaneous insulin infusion (CSII)

Pump or infusion set malfunctions can lead to a fast onset of hyperglycaemia and ketosis. Prompt identification and correction of the cause of hyperglycaemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required.

Concomitant illness

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

Combination of thiazolidinediones and insulin medicinal products

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

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 glycaemic control decreases the risk of diabetic retinopathy and neuropathy.

Insulin antibodies

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

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 this medicinal product and other insulin medicinal products.

Patients must visually verify the units of the dose prior to administering. 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.

Travelling between time zones

Before travelling between different time zones, the patient should seek the doctor's advice.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

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

The following substances may reduce insulin requirement:

Oral antidiabetics, monoamine oxidase inhibitors (MAOIs), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids, sulphonamides and GLP-1 receptor agonist.

The following substances may increase insulin requirement:

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

Beta-blocking agents may mask the symptoms of hypoglycaemia.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Fiasp can be used in pregnancy.

Data from two randomised controlled clinical trials conducted with insulin aspart (322 + 27 exposed pregnancies) do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/new born when compared to soluble human insulin.

Intensified blood glucose control and monitoring of pregnant women with diabetes (type 1 diabetes, type 2 diabetes or 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.

Breast-feeding

There are no restrictions on treatment with Fiasp during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the dosage may need to be adjusted.

Fertility

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

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or using machines).

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

4.8 Undesirable effects

Summary of safety profile

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

Tabulated list of adverse reactions

Adverse reactions listed below (Table 2) are based on data from 6 completed therapeutic confirmatory trials in adults. Frequency categories are defined according to the following convention: Very common

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

Table 2 Adverse reactions from clinical trials

MedDRA System Organ Class	Very common	Common	Uncommon	Not known
Immune system disorders			Hypersensitivity	Anaphylactic reactions
Metabolism and nutrition disorders	Hypoglycaemia			
Skin and subcutaneous tissue disorders		Allergic skin manifestations	Lipodystrophy	
General disorders and administration site conditions		Injection/infusion site reactions		

Description of selected adverse reactions

Allergic reactions

Allergic skin manifestations reported with Fiasp (1.8% vs. 1.5% for comparator) include eczema, rash, rash pruritic, urticaria and dermatitis.

With Fiasp generalised hypersensitivity reactions (manifested by generalised skin rash and facial oedema) was reported uncommonly (0.2% vs. 0.3% for comparator).

Hypoglycaemia

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation (see sections 4.4 and 5.1). Hypoglycaemia may occur earlier after an injection/infusion of Fiasp compared to other mealtime insulins due to the earlier onset of action.

Lipodystrophy

Lipodystrophy (including lipohypertrophy, lipoatrophy) was reported at the injection/infusion site in patients treated with Fiasp (0.5% vs. 0.2% in comparator). Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

Injection/infusion site reactions

Injection site reactions (including rash, redness, inflammation, pain and bruising) were reported in patients treated with Fiasp (1.3% vs. 1.0% in comparator). In patients using CSII (N=261): Infusion site reactions (including redness, inflammation, irritation, pain, bruising and itching) were reported in patients treated with Fiasp (10.0% vs. 8.3% in comparator). These reactions are usually mild and transitory and they normally disappear during continued treatment.

Paediatric population

Safety and efficacy have been investigated in a therapeutic confirmatory trial in children with type 1 diabetes aged 2 to less than 18 years. In the trial, 519 patients were treated with Fiasp. Overall the frequency, type and severity of adverse reactions in the paediatric 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 this study with paediatric patients compared to studies in adults (see above). In the paediatric population lipodystrophy was reported with a frequency of 2.1% for Fiasp vs. 1.6% for NovoRapid.

Other special populations

Based on results from clinical trials with insulin aspart in general, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population. The safety profile in very elderly patients (≥ 75 years) or patients with moderate to severe renal impairment or hepatic impairment is limited. Fiasp has been administered to elderly patients for the investigation of pharmacokinetic properties (see section 5.2).

Reporting of suspected adverse reactions

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

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, fast-acting
ATC code: A10AB05.

Mechanism of action

Fiasp is a fast-acting insulin aspart formulation.

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. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Pharmacodynamic effects

Fiasp is a mealtime insulin aspart formulation in which the addition of nicotinamide (vitamin B₃) results in a faster initial absorption of insulin compared to NovoRapid.

The onset of action was 5 minutes earlier and time to maximum glucose infusion rate was 11 minutes earlier with Fiasp than with NovoRapid. The maximum glucose-lowering effect of Fiasp occurred between 1 and 3 hours after injection. The glucose-lowering effect during the first 30 minutes

(AUC_{GIR, 0–30 min}) was 51 mg/kg with Fiasp and 29 mg/kg with NovoRapid (Fiasp/NovoRapid ratio: 1.74 [1.47;2.10]_{95% CI}). The total glucose-lowering effect and maximum (GIR_{max}) glucose-lowering effect were comparable between Fiasp and NovoRapid. Total and maximum glucose-lowering effect of Fiasp increase linearly with increasing dose within the therapeutic dose range.

Fiasp has an earlier onset of action compared to NovoRapid (see section 5.2), leading to a subsequent increased glucose-lowering effect. This must be considered when prescribing Fiasp.

The duration of action was shorter for Fiasp compared to that of NovoRapid and lasted for 3–5 hours.

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

Clinical efficacy and safety

Fiasp has been studied in 2,068 adult patients with type 1 diabetes (1,143 patients) and type 2 diabetes (925 patients) in 3 randomised efficacy and safety trials (18–26 weeks of treatment). Furthermore, Fiasp has been studied in 777 paediatric subjects with type 1 diabetes in a randomised efficacy and safety trial (26 weeks of treatment). No children below the age of 2 years were randomised in the trial.

Patients with type 1 diabetes mellitus

The treatment effect of Fiasp in achieving glycaemic control was assessed when administered at mealtime or postmeal. Fiasp administered at mealtime was non-inferior to NovoRapid in reducing HbA_{1c}, and the improvement in HbA_{1c} was statistically significant in favour of Fiasp. Fiasp administered postmeal achieved similar HbA_{1c} reduction as NovoRapid dosed at mealtime (Table 3).

Table 3 Results from 26 week basal-bolus clinical trial in patients with type 1 diabetes

	Fiasp mealtime + insulin detemir	Fiasp postmeal + insulin detemir	NovoRapid mealtime + insulin detemir
N	381	382	380
HbA_{1c} (%)			
Baseline → End of trial	7.6 → 7.3	7.6 → 7.5	7.6 → 7.4
Adjusted change from baseline	-0.32	-0.13	-0.17
<i>Estimated treatment difference</i>	<i>-0.15 [-0.23;-0.07]^{CE}</i>	<i>0.04 [-0.04;0.12]^D</i>	
HbA_{1c} (mmol/mol)			
Baseline → End of trial	59.7 → 56.4	59.9 → 58.6	59.3 → 57.6
Adjusted change from baseline	-3.46	-1.37	-1.84
<i>Estimated treatment difference</i>	<i>-1.62 [-2.50;-0.73]^{CE}</i>	<i>0.47 [-0.41;1.36]^D</i>	
2-hour postmeal glucose increment (mmol/L)^A			
Baseline → End of trial	6.1 → 5.9	6.1 → 6.7	6.2 → 6.6
Adjusted change from baseline	-0.29	0.67	0.38
<i>Estimated treatment difference</i>	<i>-0.67 [-1.29;-0.04]^{CE}</i>	<i>0.30 [-0.34;0.93]^D</i>	
1-hour postmeal glucose increment (mmol/L)^A			
Baseline → End of trial	5.4 → 4.7	5.4 → 6.6	5.7 → 5.9
Adjusted change from baseline	-0.84	1.27	0.34
<i>Estimated treatment difference</i>	<i>-1.18 [-1.65;-0.71]^{CE}</i>	<i>0.93 [0.46;1.40]^D</i>	
Bodyweight (kg)			
Baseline → End of trial	78.6 → 79.2	80.5 → 81.2	80.2 → 80.7
Adjusted change from baseline	0.67	0.70	0.55
<i>Estimated treatment difference</i>	<i>0.12 [-0.30;0.55]^C</i>	<i>0.16 [-0.27;0.58]^D</i>	
Observed rate of severe or BG confirmed hypoglycaemia^B per patient year of exposure (percentage of patients)			
	59.0 (92.7)	54.4 (95.0)	58.7 (97.4)
<i>Estimated rate ratio</i>	<i>1.01 [0.88;1.15]^C</i>	<i>0.92 [0.81;1.06]^D</i>	

Baseline, End of trial values are based on the mean of the observed last available values. The 95% confidence interval is stated in '[]'

^A Meal test

^B Severe hypoglycaemia (episode requiring assistance of another person) or blood glucose (BG) confirmed hypoglycaemia defined as episodes confirmed by plasma glucose < 3.1 mmol/L irrespective of symptoms

^C The difference is for Fiasp mealtime – NovoRapid mealtime

^D The difference is for Fiasp postmeal – NovoRapid mealtime

^E Statistically significant in favour of Fiasp mealtime

33.3% of patients treated with mealtime Fiasp reached a target HbA_{1c} of < 7% compared to 23.3% of patients treated with postmeal Fiasp and 28.2% of patients treated with mealtime NovoRapid. The estimated odds of achieving HbA_{1c} < 7% were statistically significantly greater with mealtime Fiasp than with mealtime NovoRapid (odds ratio: 1.47 [1.02; 2.13]_{95% CI}). No statistical significant difference was shown between postmeal Fiasp and mealtime NovoRapid.

Fiasp administered at mealtime provided significantly lower 1-hour and 2-hour postmeal glucose increment compared to NovoRapid administered at mealtime. Fiasp administered postmeal resulted in higher 1-hour postmeal glucose increment and comparable 2-hour postmeal glucose increment to NovoRapid dosed at mealtime (Table 3).

Median total bolus insulin dose at trial end was similar for mealtime Fiasp, postmeal Fiasp and mealtime NovoRapid (change from baseline to end of trial: mealtime Fiasp: 0.33→0.39 units/kg/day; postmeal Fiasp: 0.35→0.39 units/kg/day; and mealtime NovoRapid: 0.36→0.38 units/kg/day). Changes in median total basal insulin dose from baseline to end of trial were comparable for mealtime Fiasp (0.41→0.39 units/kg/day), postmeal Fiasp (0.43→0.42 units/kg/day) and mealtime NovoRapid (0.43→0.43 units/kg/day).

Patients with type 2 diabetes mellitus

The reduction in HbA_{1c} from baseline to end of trial was confirmed to be non-inferior to that obtained with NovoRapid (Table 4).

Table 4 Results from 26 week basal-bolus clinical trial in patients with type 2 diabetes

	Fiasp + insulin glargine	NovoRapid + insulin glargine
N	345	344
HbA_{1c} (%)		
Baseline → End of trial	8.0 → 6.6	7.9 → 6.6
Adjusted change from baseline	-1.38	-1.36
<i>Estimated treatment difference</i>		-0.02[-0.15;0.10]
HbA_{1c} (mmol/mol)		
Baseline → End of trial	63.5 → 49.0	62.7 → 48.6
Adjusted change from baseline	-15.10	-14.86
<i>Estimated treatment difference</i>		-0.24 [-1.60;1.11]
2-hour postmeal glucose increment (mmol/L)^A		
Baseline → End of trial	7.6 → 4.6	7.3 → 4.9
Adjusted change from baseline	-3.24	-2.87
<i>Estimated treatment difference</i>		-0.36 [-0.81;0.08]
1-hour postmeal glucose increment (mmol/L)^A		
Baseline → End of trial	6.0 → 4.1	5.9 → 4.6
Adjusted change from baseline	-2.14	-1.55
<i>Estimated treatment difference</i>		-0.59 [-1.09;-0.09] ^C
Bodyweight (kg)		
Baseline → End of trial	89.0 → 91.6	88.3 → 90.8
Adjusted change from baseline	2.68	2.67
<i>Estimated treatment difference</i>		0.00 [-0.60;0.61]

Observed rate of severe or BG confirmed hypoglycaemia^B per patient year of exposure (percentage of patients)	17.9 (76.8)	1.09 [0.88;1.36]	16.6 (73.3)
<i>Estimated rate ratio</i>			

Baseline, End of trial values are based on the mean of the observed last available values. The 95% confidence interval is stated in '[]'

^A Meal test

^B Severe hypoglycaemia (episode requiring assistance of another person) or blood glucose (BG) confirmed hypoglycaemia defined as episodes confirmed by plasma glucose < 3.1 mmol/L irrespective of symptoms

^C Statistically significant in favour of Fiasp

Postmeal dosing has not been investigated in patients with type 2 diabetes.

74.8% of patients treated with Fiasp reached a target HbA_{1c} of < 7% compared to 75.9% of patients treated with NovoRapid. There was no statistical significant difference between Fiasp and NovoRapid in the estimated odds of achieving HbA_{1c} < 7%.

Median total bolus insulin dose at trial end was similar for Fiasp and NovoRapid (change from baseline to end of trial: Fiasp: 0.21→0.49 units/kg/day and NovoRapid: 0.21→0.51 units/kg/day). Changes in median total basal insulin dose from baseline to end of trial were comparable for Fiasp (0.56→0.53 units/kg/day) and NovoRapid (0.52→0.48 units/kg/day).

Elderly

In the three controlled clinical studies, 192 of 1,219 (16%) Fiasp treated patients with type 1 diabetes or type 2 diabetes were ≥ 65 years of age and 24 of 1,219 (2%) were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Continuous subcutaneous insulin infusion (CSII)

A 6-week, randomised (2:1), double-blind, parallel-group, active controlled trial evaluated compatibility of Fiasp and NovoRapid administered via CSII system in adult patients with type 1 diabetes. There were no microscopically confirmed episodes of infusion set occlusions in either the Fiasp (N=25) or NovoRapid (N=12) groups. There were two patients from the Fiasp group who each reported two treatment-emergent infusion site reactions.

In a 2-week cross-over trial, Fiasp showed a greater postmeal glucose-lowering effect after a standardised meal test with regard to 1-hour and 2-hour postmeal glucose response (treatment difference: -0.50 mmol/L [-1.07; 0.07]_{95% CI} and -0.99 mmol/L [-1.95; -0.03]_{95% CI}), respectively compared to NovoRapid in a CSII setting.

Paediatric population

The efficacy and safety of Fiasp have been studied in a 1:1:1 randomised active controlled clinical trial in children and adolescents with type 1 diabetes, aged 1 to 18 years, for a period of 26 weeks (N=777). In this trial the efficacy and safety of Fiasp administered at mealtime (0–2 minutes before meal) or postmeal (20 minutes after meal start) and NovoRapid administered at mealtime, both used in combination with insulin degludec, were compared.

Patients in the Fiasp mealtime arm included 16 children aged 2–5 years, 100 children aged 6–11 years and 144 adolescents aged 12–17 years. Patients in the Fiasp postmeal arm included 16 children aged 2–5 years, 100 children aged 6–11 years and 143 adolescents aged 12–17 years.

Fiasp administered at mealtime showed superior glycaemic control compared to NovoRapid mealtime with regards to change in HbA_{1c} (ETD: -0.17% [-0.30; -0.03]_{95% CI}). Fiasp administered postmeal showed non-inferior glycaemic control compared to NovoRapid mealtime (ETD: 0.13% [-0.01; 0.26]_{95% CI}).

Fiasp mealtime showed a statistically significant improvement in 1–hour postmeal glucose increment mean over all three main meals compared to NovoRapid (measured by SMPG). For Fiasp postmeal this comparison favoured NovoRapid mealtime.

No overall increased risk of severe or blood glucose confirmed hypoglycaemia was observed compared to NovoRapid.

The observed effects and the safety profiles were comparable between all age groups.

5.2 Pharmacokinetic properties

Absorption

Fiasp is a mealtime insulin aspart formulation in which the addition of nicotinamide (vitamin B₃) results in a faster initial absorption of insulin. Insulin appeared in the circulation approximately 4 minutes after administration (Figure 1). The onset of appearance was twice as fast (corresponding to 5 minutes earlier), time to 50% maximum concentration was 9 minutes shorter with Fiasp compared to NovoRapid with four times as much insulin available during first 15 minutes and with twice as much insulin available during the first 30 minutes.

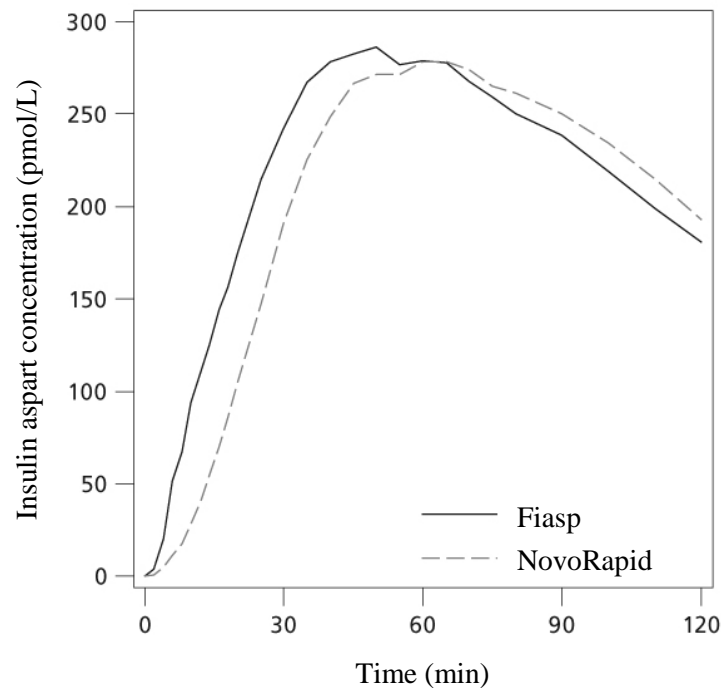


Figure 1 Mean insulin profile in patients with type 1 diabetes after subcutaneous injection.

The total insulin exposure was comparable between Fiasp and NovoRapid. The mean C_{max} for a dose of 0.2 units/kg body weight is 298 pmol/L and comparable to NovoRapid.

Total exposure and maximum insulin concentration increases proportionally with increasing subcutaneous dose of Fiasp within the therapeutic dose range.

The absolute bioavailability of insulin aspart after subcutaneous administration of Fiasp in the abdomen, deltoid and thigh was approximately 80%.

After administration of Fiasp, the fast onset of appearance is maintained regardless of injection site. Time to maximum concentration and total insulin aspart exposure were all comparable between the abdomen, upper arm and the thigh. Early insulin exposure and maximum concentration were comparable for the abdomen and upper arm regions, but lower for the thigh.

Continuous subcutaneous insulin infusion (CSII)

The onset of exposure in a CSII setting (time to reach maximum concentration) was 26 minutes shorter with Fiasp compared to NovoRapid resulting in approximately three times as much insulin available during the first 30 minutes (Figure 2).

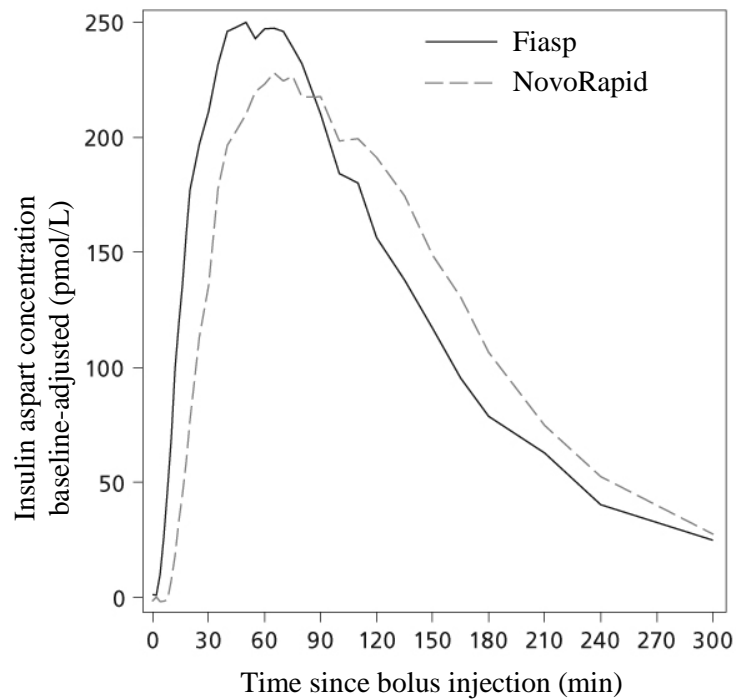


Figure 2 Mean insulin profiles in patients with type 1 diabetes in a CSII setting (0–5 hours) corrected for basal insulin infusion

Distribution

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

Volume of distribution (V_d) after intravenous administration was 0.22 L/kg (e.g., 15.4 L for a 70 kg subject) corresponding to the extracellular fluid volume in the body.

Biotransformation

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

Elimination

Half-life after subcutaneous administration of Fiasp is 57 minutes and comparable to NovoRapid.

Following intravenous administration of Fiasp, clearance was rapid (1.0 L/h/kg) and the elimination half-life was 10 minutes.

Special populations

Elderly

In elderly 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.

Total insulin aspart exposure and maximum concentration following administration of Fiasp was 30% higher in elderly subjects compared to younger adult subjects.

Gender

The effect of gender on the pharmacokinetics of Fiasp was examined in an across-trial analysis of the pharmacokinetic 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 females and male patients with type 1 diabetes.

The early and maximum insulin exposure of Fiasp was comparable for female and male patients with type 1 diabetes. However, total insulin exposure was larger in female compared to male patients with type 1 diabetes.

Obesity

The initial absorption rate was slower with increasing BMI while the total exposure was similar across different BMI levels. Compared to NovoRapid, the influence of BMI on the absorption was less pronounced for Fiasp leading to relatively higher initial exposure.

Race and Ethnicity

The effect of race and ethnicity (Blacks vs. Whites and Hispanics vs. non-Hispanics) on the total insulin exposure of Fiasp was based on results from a population pharmacokinetic analysis in patients with type 1 diabetes. For Fiasp no difference in exposure was found between the racial and ethnic groups investigated.

Hepatic impairment

A single dose pharmacokinetic study of insulin aspart was performed with NovoRapid in 24 subjects with hepatic function ranging from normal to severely impaired. In subjects with hepatic impairment, absorption rate was decreased and more variable.

Renal impairment

A single dose pharmacokinetic study of insulin aspart was performed with NovoRapid in 18 subjects with renal function ranging from normal to severely impaired. No apparent effect of creatinine clearance values on AUC, C_{max}, CL/F and T_{max} of insulin aspart was found. Data were limited in patients with moderate and severe renal impairment. Patients with renal failure necessitating dialysis treatment were not investigated.

Paediatric population

In children (6–11 years) and adolescents (12–18 years) 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 children and adolescents to that in adults. Total exposure of Fiasp was lower in children and adolescents compared to adults when dosed with 0.2 units/kg body weight, while the maximum serum insulin aspart concentration was similar between age groups.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction after exposure to insulin aspart. In *in vitro* tests, including binding to insulin and IGF-1 receptor sites and effects on cell growth, insulin aspart behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of insulin aspart is equivalent to human insulin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol
Metacresol
Glycerol

Zinc acetate
Disodium phosphate dihydrate
Arginine hydrochloride
Nicotinamide (vitamin B₃)
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

The medicinal product must not be diluted or mixed with any other medicinal products except infusion fluids as described in section 4.2.

6.3 Shelf life

30 months.

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

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

Fiasp 100 units/mL solution for injection in cartridge

After first opening or carried as a spare, the medicinal product may be stored for a maximum of 4 weeks. Do not store above 30°C. Do not refrigerate. Do not freeze. If cartridge is carried as a spare and unused, the cartridge should be kept in the outer carton in order to protect from light.

Fiasp 100 units/mL solution for injection in vial

After first opening, the medicinal product may be stored for a maximum of 4 weeks (including time in a pump reservoir, see section 6.6). Do not store above 30°C. Can be stored in the refrigerator (2°C–8°C). Do not freeze. Keep the vial in outer carton in order to protect from light.

6.4 Special precautions for storage

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

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

Fiasp 100 units/mL solution for injection in cartridge

Store in a refrigerator (2°C–8°C). Do not freeze. Keep away from the freezing element. Keep the cartridge in the outer carton in order to protect from light.

Fiasp 100 units/mL solution for injection in vial

Store in a refrigerator (2°C–8°C). Do not freeze. Keep away from the freezing element. Keep the vial in the outer carton in order to protect from light.

After first opening or carried as a spare, see section 6.3.

6.5 Nature and contents of container

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

Cartridge (type 1 glass) with a plunger (halobutyl) and a stopper (halobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

Each pre-filled pen contains 3 mL of solution.

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

Fiasp 100 units/mL solution for injection in cartridge

Cartridge (type 1 glass), with a plunger (halobutyl) and a stopper (halobutyl/polyisoprene) in a carton.
Each cartridge contains 3 mL of solution.
Pack sizes of 5 and 10 cartridges.

Fiasp 100 units/mL solution for injection in vial

Vial (type 1 glass) closed with a halobutyl/polyisoprene rubber disc and a protective plastic cap in order to obtain a tamper-proof container in a carton.
Each vial contains 10 mL of solution.
Pack sizes of 1 vial, 5 vials and a multipack containing 5 (5 packs of 1) vials.

6.6 Special precautions for disposal and other handling

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

Fiasp which has been frozen must not be used.

The patient should discard the needle after each injection.

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

Needles and pre-filled pens must not be shared. The cartridge must not be refilled.

Fiasp 100 units/mL solution for injection in cartridge

Needles and cartridges must not be shared. The cartridge must not be refilled.

Fiasp 100 units/mL solution for injection in vial

Needles and syringes must not be shared.

Fiasp may be used in an infusion pump (CSII) for a maximum of 6 days, as described in section 4.2 and in the package leaflet. Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/16/1160/001
EU/1/16/1160/002
EU/1/16/1160/003
EU/1/16/1160/004
EU/1/16/1160/005
EU/1/16/1160/006
EU/1/16/1160/007
EU/1/16/1160/008
EU/1/16/1160/009

EU/1/16/1160/010
EU/1/16/1160/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 January 2017

10. DATE OF REVISION OF THE TEXT

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