

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

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

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.

*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).

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults.

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 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.

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 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 has 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

The safety and efficacy of Fiasp in children and adolescents below 18 years of age have not been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.

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 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.

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

To be used as prescribed by doctor only. If experience dizziness or fainting, please consult your doctor immediately.

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 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.

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.

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 clinical trial data from phase 3 trials consisting of 4 completed therapeutic confirmatory trials including one continuous subcutaneous insulin infusion (CSII) trial. 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
Immune system disorders			Hypersensitivity
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 (1.5% vs. 1.4% 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. 0.1% for comparator). Anaphylactic reactions have not been reported with Fiasp. With insulin preparations in general, anaphylactic reactions may occur. Immediate-type allergic reactions to either insulin itself or the excipients may potentially be life-threatening.

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 section 4.4 and 5.1). Hypoglycaemia may occur earlier after an injection 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 (0.2% vs. 0% 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/infusion site reactions (including rash, redness, inflammation, bruising, and itching) was reported in patients treated with Fiasp (1.0% vs. 0.7% in comparator). These reactions are usually mild and transitory and they normally disappear during continued treatment.

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**

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 ($AUC_{GIR, 0-30 \text{ min}}$) 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.

The duration of action was shorter for Fiasp compared to that of NovoRapid, and lasts 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 randomised adult patients with type 1 diabetes mellitus (1,143 patients) and type 2 diabetes mellitus (925 patients) in 3 efficacy and safety trials (18–26 weeks of treatment).

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>	-0.15 [-0.23;-0.07] ^{CE}	0.04 [-0.04;0.12] ^D	
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>	-1.62 [-2.50;-0.73] ^{CE}	0.47[-0.41;1.36] ^D	
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>	-0.67 [-1.29;-0.04] ^{CE}	0.30 [-0.34;0.93] ^D	
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>	-1.18[-1.65;-0.71] ^{CE}	0.93[0.46;1.40] ^D	
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>	0.12 [-0.30;0.55] ^C	0.16 [-0.27;0.58] ^D	
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>	1.01 [0.88;1.15] ^C	0.92 [0.81;1.06] ^D	

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>		<i>-0.02[-0.15;0.10]</i>
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>		<i>-0.24 [-1.60;1.11]</i>
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>		<i>-0.36 [-0.81;0.08]</i>
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>		<i>-0.59 [-1.09;-0.09]^C</i>
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>		<i>0.00 [-0.60;0.61]</i>
Observed rate of severe or BG confirmed hypoglycaemia^B per patient year of exposure (percentage of patients)		
	17.9 (76.8)	16.6 (73.3)
<i>Estimated rate ratio</i>		<i>1.09 [0.88;1.36]</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 mellitus.

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 mellitus or type 2 diabetes mellitus 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.

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.

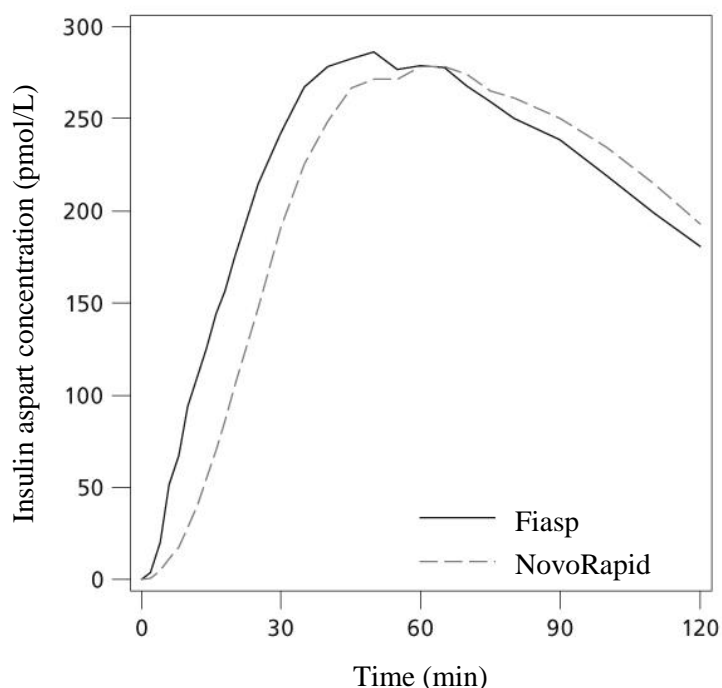


Figure 1 Mean insulin profile in patients with type 1 diabetes after subcutaneous injection.

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.

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 versus Whites and Hispanics versus 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.

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. At the end of this period the pen should be used or discarded. 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.

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.

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 5 (without needles) pre-filled pens.

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.

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

Importer

Novo Nordisk Pharma (Thailand) Ltd., Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBERS

Thai registration number

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Approval date from Thai FDA

10. DATE OF REVISION OF THE TEXT

Approval date from Thai FDA

Detailed information on this medicinal product is available on the website of the Thai FDA

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 high or 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.

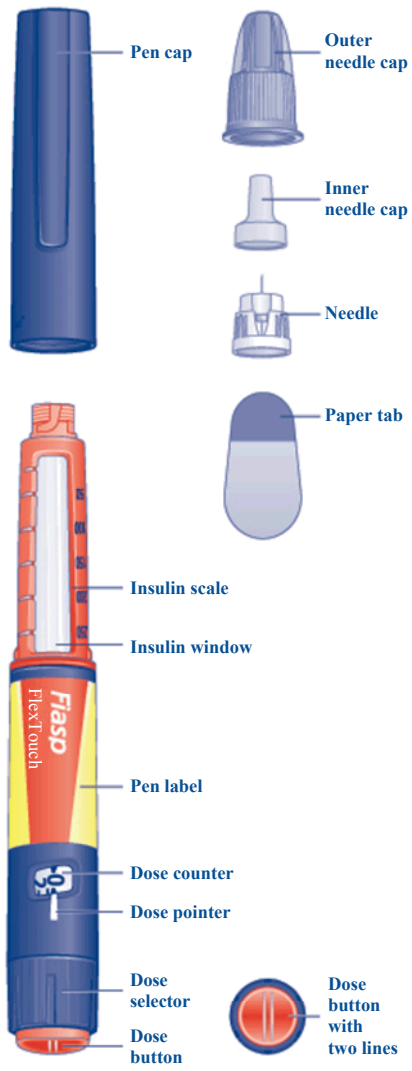
If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the FlexTouch pre-filled pen.

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

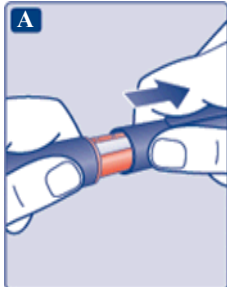
Pay special attention to these notes as they are important for correct use of the pen.

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

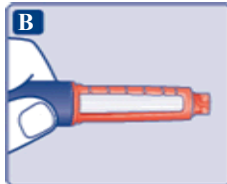


1 Prepare your pen with a new needle

- **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.**



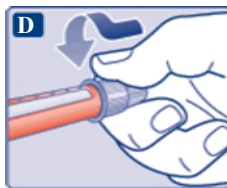
- **Check that the insulin in your pen is clear** and colourless. Look through the insulin window. If the insulin looks cloudy, do not use the pen.



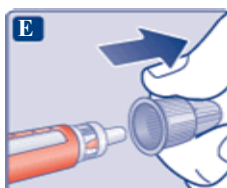
- **Take a new needle** and tear off the paper tab.



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



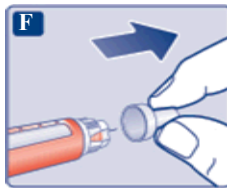
- **Pull off the outer needle cap and keep it for later.** You will need it after the injection, to safely remove the needle from the pen.



- **Pull off the inner needle cap and throw it away.** If you try to put it back on, you may accidentally prick or injure 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 for your injection.



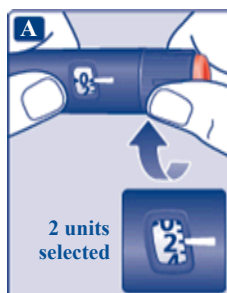
⚠ Always use a new needle for each injection.

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

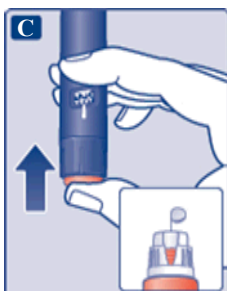
- **Always check the insulin flow before you start.**
This helps you to ensure that you get your full insulin dose.
- Turn the dose selector to **select 2 units. Make sure the dose counter shows 2.**



- 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 2A to 2C up to 6 times. If there is still no drop, change the needle and repeat steps 2A to 2C 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 is flowing properly.

If no drop appears, no insulin will be injected, 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 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.

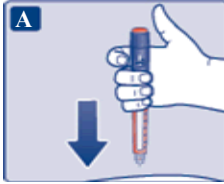
! **Always use the dose counter and the dose pointer to see how many units you have selected before injecting the insulin.**

Do **not** count the pen clicks to set the dose. If you select and inject the wrong dose, your blood sugar level may get too high or too low.

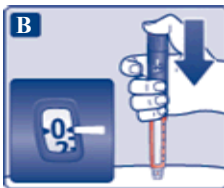
Do not use the insulin scale, it only shows approximately how much insulin is left in your pen. The dose selector clicks differently when turned forwards, backwards or past the number of units left.

4 Inject your dose

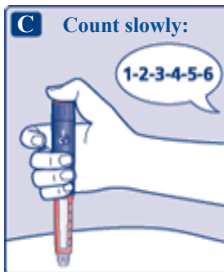
- **Insert the needle into your skin** as your doctor or nurse has shown you.
- **Make sure you can see the dose counter.**
Do not touch the dose counter with your fingers. This could interrupt the injection.



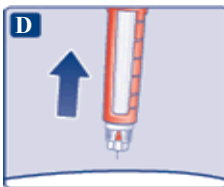
- **Press and hold down the dose button until the dose counter shows 0.**
The 0 must line up with the dose pointer. You may then hear or feel a click.



- **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 on the skin for a few minutes to stop the bleeding. 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 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?

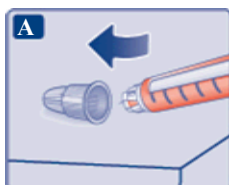
Remove the needle as described in section 5 and repeat all steps starting with section 1: Prepare your pen with a new needle. Make sure you select the full dose you need.

Never touch the dose counter when you inject.

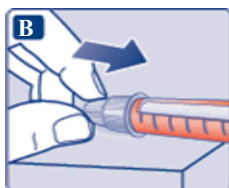
This can interrupt the injection.

5 After your injection

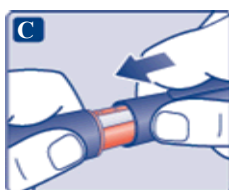
- **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer cap.



- Once the needle is covered, **carefully push the outer needle cap completely on.**
- **Unscrew the needle** and dispose of it 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.



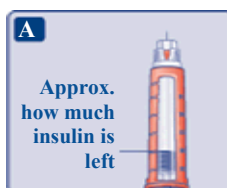
Always dispose of the needle after each injection. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing. If the needle is blocked, you will **not** inject any insulin.

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 prick or injure 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 high or low blood sugar levels.

⚠ 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 them.
- 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 high or low blood sugar levels.
- **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.