1. Name of the medicinal product

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).
Each 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

Solution for injection.
Clear, colourless, aqueous solution.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years 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 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
The suggested initial dose is 4 units at one or more meals. The 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	< 71	-1
4–6	71–108	No adjustment
> 6	> 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 sections 5.1 and 5.2). The therapeutic experience in patients ≥ 75 years of age is limited.

Renal impairment
Renal impairment may reduce the patient's insulin requirements. In patients with renal impairment, glucose monitoring should be intensified and the dose adjusted on an individual basis (see section 5.2).

Hepatic impairment
Hepatic impairment may reduce the patient's insulin requirements. In patients with 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 2 years (see section 5.1). There is no clinical experience with the use of Fiasp® in children below the age of 2 years.
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 dose.

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 by injection in the abdominal wall or the upper arm (see section 5.2). Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see sections 4.4 and 4.8).

Administration with a syringe

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

Continuous subcutaneous insulin infusion (CSII)
Fiasp® solution for injection in vial 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. 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 the 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 unit/ml insulin aspart in infusion systems – using polypropylene infusion bags. Fiasp® must not be mixed with any other insulin or any other medicinal product except those mentioned in section 6.6. For instructions on dilution of the medicinal product before administration, see section 6.6.
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
Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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
Paediatric patients with type 1 diabetes treated with mealtime and postmeal Fiasp® in combination with insulin degludec reported a higher rate of blood glucose confirmed hypoglycaemic episodes compared to patients treated with NovoRapid®; the imbalance was greater during the nocturnal period. Close

monitoring of blood glucose levels is recommended if administering this medicinal product after the start of the last meal of the day, in order to avoid nocturnal hypoglycaemia.

Hyperglycaemia and diabetic ketoacidosis
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 are necessary. Interim therapy with subcutaneous injection may be required.

Skin and subcutaneous tissue disorders
Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic 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 hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medicinal products may be considered.

Transfer from other insulin medicinal products
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human insulin or human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. Patients transferred to Fiasp® from another type of insulin may require a change in dose from that used with their usual insulin medicinal products.

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 the insulin. 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, that is to say 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, sulfonamides and GLP-1 receptor agonists.

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/newborn 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 breast-feeding mother presents no risk to the baby. However, the dose 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 the safety profile

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

Tabulated list of adverse reactions

Adverse reactions listed below are based on data from 6 completed therapeutic confirmatory trials in adults. Frequency categories are defined according to the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Very common: Hypoglycaemia.
Common: Allergic skin manifestations and injection/infusion site reactions.
Uncommon: Hypersensitivity and lipodystrophy.
Not known: Anaphylactic reactions and cutaneous amyloidosis†.
† ADR from postmarketing sources.

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) were 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.

Skin and subcutaneous tissue disorders

Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Lipodystrophy 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 given injection area may help to reduce or prevent these reactions (see section 4.4).

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 trial with paediatric patients compared to trials 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).

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 carbohydrates 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 substance 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 B_3) 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 ($AUC_{GIR,\ 0\text{-}30\ min}$) 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 early 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 ($AUC_{GIR,\ 0\text{-}1h}$, CV~26%), total ($AUC_{GIR,\ 0\text{-}12h}$, 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 2).

Table 2 Results from a 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
Estimated treatment difference	*-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
Estimated treatment difference	*-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
Estimated treatment difference	*-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
Estimated treatment difference	*-1.18 [-1.65;-0.71]*[CE]	*0.93 [0.46;1.40]*[D]	
Body weight (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
Estimated treatment difference	*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)
Estimated rate ratio	*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® administrated 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 2).

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 3).

Table 3 Results from a 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
Estimated treatment difference	*-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
Estimated treatment difference	*-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
Estimated treatment difference	*-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
Estimated treatment difference	*-0.59 [-1.09;-0.09]*[C]	
Body weight (kg)		
Baseline → End of trial	89.0 → 91.6	88.3 → 90.8
Adjusted change from baseline	2.68	2.67
Estimated treatment difference	*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)	16.6 (73.3)
Estimated rate ratio	*1.09 [0.88;1.36]*	

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 trials, 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, 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.
A higher rate of blood glucose confirmed hypoglycaemic episodes compared to patients treated with NovoRapid® was observed; the imbalance was greater during the nocturnal period.

5.2 Pharmacokinetic properties

Absorption

Fiasp® is a mealtime insulin aspart formulation in which the addition of nicotinamide (vitamin B_3) 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 the first 15 minutes and with twice as much insulin available during the first 30 minutes.

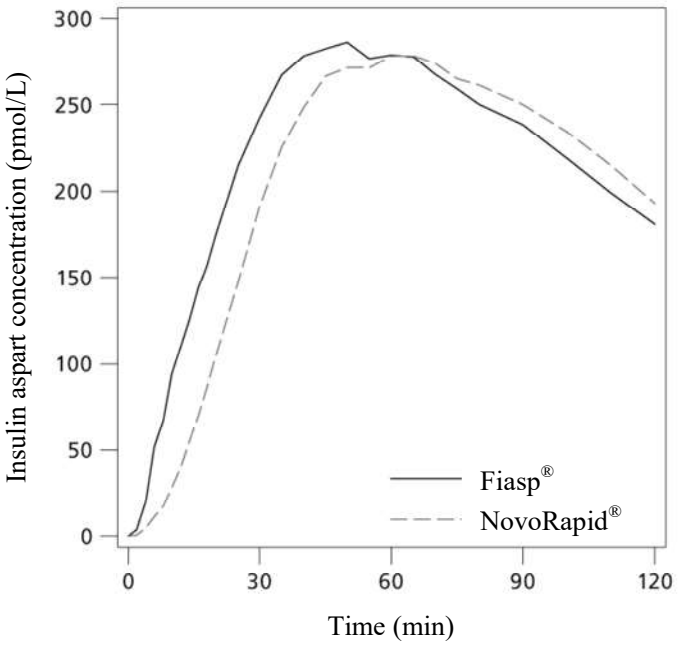

Figure 1 Mean insulin profile in patients with type 1 diabetes after subcutaneous injection

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).

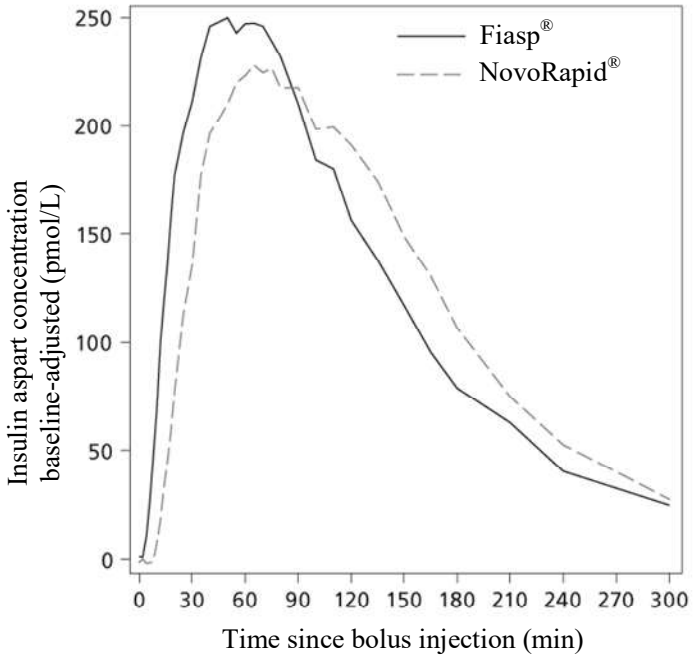

Figure 2 Mean insulin profiles in patients with type 1 diabetes in a CSII setting (0–5 hours) corrected for basal insulin infusion

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
The half-life after subcutaneous administration of Fiasp® is 57 minutes and comparable to NovoRapid®.

Following intravenous administration of Fiasp®, the clearance was rapid (1 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® were 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 trials. 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® were similar in children and adolescents to those 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 B_3), hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and 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 6.6.

6.3 Shelf life
Expiry date is stated on the pen label and carton after ‘Expiry’.

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 the outer carton in order to protect from light.

6.4 Special precautions for storage

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.

For storage conditions after first opening of the medicinal product or carried as a spare, see section 6.3.

6.5 Nature and contents of container

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. Not all pack sizes may be marketed.

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.
Needles and syringes must not be shared.

The patient should discard the needle after each injection.

Administration via CSII
When Fiasp® is drawn from a vial, it can be used in an infusion pump (CSII) for a maximum of 6 days, as described in section 4.2. Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

Intravenous use
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 for injection or 5% glucose solution for injection.
For intravenous use, it should be used at concentrations from 0.5 unit/ml to 1 unit/ml insulin aspart in infusion systems – using polypropylene infusion bags.

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

7. Product Owner

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

Fiasp® and NovoRapid® are trademarks owned by Novo Nordisk A/S, Denmark.