▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

Fiasp FlexTouch® (insulin aspart (rys)) solution for injection
Fiasp® (insulin aspart (rys)) solution for injection
Fiasp Penfill® (insulin aspart (rys)) solution for injection

1. NAME OF THE MEDICINE

Insulin aspart (rys)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin aspart is an analogue of human insulin, differing by the substitution of the amino acid proline by aspartic acid at position 28 on the B-chain. Insulin aspart is produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

1 mL of the solution contains 100 units of insulin aspart (equivalent to 3.5 mg).
FlexTouch: 1 pre-filled pen contains 3 mL equivalent to 300 units.
Vial: 1 vial contains 10 mL equivalent to 1,000 units.
Penfill: 1 cartridge contains 3 mL equivalent to 300 units.

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Sterile, clear, colourless, aqueous, ultra-fast acting solution for subcutaneous injection, subcutaneous infusion or intravenous injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Dose and Method of Administration

Dosage

Fiasp should be administered 0-2 minutes prior to starting a meal. Administration of Fiasp up to 20 minutes after starting a meal in adults was as efficacious as NovoRapid given before a meal (see section 5.1 Pharmacodynamic Properties – Clinical trials).

Fiasp can be used for continuous subcutaneous insulin infusion (CSII) in pumps or be administrated intravenously by healthcare professionals.

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.

Dosing with Fiasp is individual and determined in accordance with the needs of the patient, in particular the estimated carbohydrate consumption and glycaemic load of the meal.

The pharmacokinetic profiles of Fiasp and NovoRapid are distinct during the first hour following administration which is of particular importance for a mealtime insulin. The earlier onset of action of Fiasp and the subsequent increased glucose lowering effect compared with NovoRapid must be considered when prescribing Fiasp.

Injection therapy: Fiasp 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 remainder by intermediate acting or long-acting insulin.

CSII: Fiasp can be used for continuous subcutaneous insulin infusion (CSII) in pumps. In this case, Fiasp will cover both the need for bolus insulin (approximately 50%) and basal insulin. The timing of basal and bolus doses may require alterations when changing insulin formulations.

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

Missed dose
Patients on basal-bolus treatment who forget a mealtime dose are advised to monitor their blood glucose level to decide if an insulin dose is needed. Patients should resume their usual dosing schedule at the next meal.

Initiation
Patients with type 1 diabetes mellitus
The recommended starting dose of Fiasp in insulin naïve patients with type 1 diabetes is approximately 50% of the total daily insulin dose and should be divided between each daily meal. The remainder of the total daily insulin dose should be administered as intermediate-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.

Transfer from other insulin medicinal product
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. Due to the faster onset of insulin action, Fiasp should be injected at the start of a meal or postmeal (within 20 minutes after starting a meal).

Due to the earlier onset of action of Fiasp and the subsequent increased glucose lowering effect, transferring a patient from another type, brand or manufacturer of insulin including NovoRapid or other insulin aspart products, to Fiasp must be done under medical supervision and may result in the need for a change in dosage. Patients transferring from other insulins will require training.

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

Use in the elderly (≥ 65 years old)
The safety and efficacy of Fiasp have been established in elderly patients. Close glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis (see section 5 Pharmacological Properties).

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 Pharmacokinetic Properties).

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 Pharmacokinetic Properties).

Paediatric population
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).

Method of Administration
Fiasp comes in a prefilled pen (**FlexTouch)** designed to be used with NovoFine® or NovoFine Plus injection needles. Fiasp FlexTouch delivers 1-80 units in steps of 1 unit. Fiasp FlexTouch is colour-coded and accompanied by a package leaflet with detailed instructions for use to be followed.

Fiasp comes in a **vial** to be used with insulin syringes with the corresponding unit scale (U-100 or 100 U/mL).

Fiasp comes in a cartridge (**Penfill**) designed to be used with Novo Nordisk insulin delivery systems (**NovoPen®**) and NovoFine or NovoFine Plus injection needles.

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

Fiasp vial: Needles and syringes must not be shared.

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.

Subcutaneous injection:
Fiasp is administered subcutaneously in the abdominal wall, the upper arm or the thigh. Injection sites should be rotated within the same region in order to reduce the risk of

lipodystrophy and cutaneous amyloidosis (see sections 4.4 Special Warnings and Precautions for Use and 4.8 Adverse Effects).
The duration of action of Fiasp may vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Continuous Subcutaneous Insulin Infusion (CSII):
Fiasp can be used for Continuous Subcutaneous Insulin Infusion (CSII) in pumps suitable for insulin infusion. Fiasp can be administered in accordance with the instructions provided by the pump manufacturer, preferably in the abdomen. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy. When used with an insulin infusion pump, Fiasp should not be diluted or mixed with any other insulin products.

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

Insulin pumps manufactured by Medtronic and Animas have been used in clinical or *in vitro* studies.

- MiniMed Paradigm 515/715
- MiniMed Paradigm 522/ 722 REAL-time
- MiniMed Paradigm 523/723 REAL-time Revel
- Animas Vibe

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 Fiasp should be used at concentrations from 0.5 unit/mL to 1.0 unit/mL insulin aspart in infusion systems using polypropylene infusion bags. Fiasp has been shown to be stable at room temperature for 24 hours in the infusion fluids such as 0.9% sodium chloride or 5% dextrose. 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.

Dosage Adjustment
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. 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.

Patients with type 2 diabetes mellitus
Fiasp adjustment may be considered daily based on mealtime and bedtime SMPG on the previous day according to Table 1.

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

Table 1 **Dose adjustment for adult patients**

Mealtime or bedtime plasma glucose		**Dose adjustment**
mmol/L		Unit
< 4.0		-1
4.0 - 6.0		No adjustment
> 6.0		+1

4.3 Contraindications

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

4.4 Special Warnings and Precautions for Use

Regular blood glucose monitoring is essential in patients on intensive insulin therapy and when there is a change in insulin type or dose.

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 Adverse Effects and 4.9 Overdose.)

Patients who have frequent hypoglycaemia or asymptomatic hypoglycaemia may require a reduction in insulin dose or a change in glycaemic targets. 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 longstanding diabetes or who have frequent episodes of hypoglycaemia.

The timing of hypoglycaemia usually reflects the time-action profile of the administered insulin formulation. Fiasp has a distinct time action profile (see section 5 Pharmacologic Properties), which impacts the timing of hypoglycaemia. A consequence of the pharmacodynamics of Fiasp is that if hypoglycaemia occurs, it may occur earlier after an injection/infusion when compared to other mealtime insulins.

The fast onset of action should be considered in patients with delayed gastric emptying.

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

Paediatric population

Closer monitoring of blood glucose levels in the evening and before bedtime 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.

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 medications may be considered.

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.

Transfer from other insulin medicinal products
See section 4.2 Dose and Method of Administration.

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 Fiasp and other insulin products.

Patients must visually verify the units of the dose prior to administering Fiasp. Therefore, the requirement for patients to self-administer is that they can read the dose scale. Patients, who are blind or have poor vision, must be instructed to always get assistance from another person who has good vision and is trained in administration of insulins.

Use in 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 Pharmacokinetic Properties).

Use in 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 Pharmacokinetic Properties).

Use in elderly
The safety and efficacy of Fiasp have been established in elderly patients. Close glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis (see section 5 Pharmacological Properties).

Paediatric use
The efficacy and safety of Fiasp in children below 1 year of age have not been established.

Effects on laboratory tests
No data available.

4.5 Interaction with Other Medicines and Other Forms of Interactions

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

The following substances may reduce insulin requirement:
Oral antidiabetic products, monoamine oxidase inhibitors (MAOIs), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids, sulphonamides 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

Effects on fertility
In reproductive toxicity studies, insulin aspart did not affect the fertility of male and female rats but caused a slight increase in pre-implantation loss at subcutaneous doses greater than 10U/kg/day. Similar effects were seen with human insulin.

Use in pregnancy
Pregnancy Category: A

Fiasp can be used in pregnancy. Data from two randomised controlled clinical trials conducted with insulin aspart (157 + 14 insulin aspart-exposed pregnancies, respectively) 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.

Use in lactation
Although no clinical trial data are available with insulin aspart products during lactation, there are no restrictions on treatment with Fiasp during breast-feeding. Insulin treatment of the nursing mother should not affect the baby. However, the Fiasp dosage may need to be adjusted.

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 operating machinery). 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 Adverse Effects (Undesirable Effects)

Summary of safety profile
The most frequently reported adverse drug reaction (ADR) during treatment with insulin, including Fiasp, is hypoglycaemia (see section Description of selected ADRs below).

Adverse events from clinical trials

Table 2 Treatment emergent adverse events (excluding hypoglycaemia[A]) reported in ≥1% of patients on Fiasp and more frequently than in patients on comparator

System Organ Class Preferred Term	**Fiasp** **N = 1244** **%**	**Comparator[B]** **N = 853** **%**
Infections and infestations		
Nasopharyngitis	13.4	12.8
Urinary tract infection	4.1	3.4
Gastroenteritis	2.3	1.5
Gastrointestinal disorders		
Nausea	3.6	2.8
Toothache	2.0	1.6
Abdominal pain upper	1.5	0.6
Musculoskeletal and connective tissue disorders		
Back pain	3.2	2.3
Arthralgia	2.1	1.6
Pain in extremity	1.5	1.3
General disorders and administration site conditions		
Fatigue	1.4	0.8
Nervous system disorders		
Dizziness	1.4	0.6
Blood and lymphatic system disorders		
Anaemia	1.3	0.6
Eye disorders		
Diabetic retinopathy	1.2	0.9
Vascular disorders		
Hypertension	1.2	0.7
Injury, poisoning and procedural complications		
Fall	1.2	0.7

Investigations		
Weight increased	1.2	0.6

[A] Hypoglycaemia (System Organ Class: Metabolism and nutrition disorders) was reported in Fiasp and comparator groups with a frequency of 'very common' (≥1/10)
[B] NovoRapid or basal insulin (insulin glargine, insulin detemir or NPH)

Adverse reactions listed below are based on post-marketing source data and classified according to MedDRA System Organ Class.

Skin and subcutaneous tissue disorders	Not known – Cutaneous amyloidosis*

*see 'Description of selected ADRs'

Tabulated list of adverse reactions
Adverse reactions (ADRs) listed below are considered expected with the medicinal product.

Less common ADRs from clinical trials (<1%)
Adverse reactions are listed by system organ class using the frequency category 'uncommon' (≥1/1,000 to <1/100).

Immune system disorders: Uncommon – hypersensitivity
Skin and subcutaneous tissue disorders: Uncommon – lipodystrophy

ADRs from post-marketing sources
No additional types of adverse reactions have been identified during post-marketing use.

Description of selected ADRs
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). Based on post-marketing data, serious forms of systemic allergic 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 concentrating, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

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 Special Warnings and Precautions for Use).

Injection/infusion site reactions
As with any insulin therapy, injection site reactions (including rash, redness, inflammation, pain and bruising) were reported in patients treated with Fiasp (1.3% vs. 1.0% in comparator). 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 transient and they normally disappear during continued treatment.

Paediatric population
Fiasp has been administered to children and adolescents from 6 years up to 18 years of age for the investigation of pharmacokinetic properties (see section 5 Pharmacological Properties). Safety and efficacy have been investigated in a therapeutic confirmatory trial in children with type 1 diabetes mellitus aged 2 to less than 18 years. In the trial, 519 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 paediatric patients compared to adults. In the paediatric population lipodystrophy was reported with a frequency of 2.1% for Fiasp vs. 1.6% for NovoRapid.

Additional information on paediatric patients is provided in Table 6, see section 5.1 Pharmacodynamic Properties – Clinical Trials.

Other special populations
Based on results from clinical trials, the frequency, type and severity of ADRs 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. Fiasp has been administered to elderly patients for the investigation of pharmacokinetic properties (see section 5 Pharmacological Properties).

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose
ADRs listed in this section are considered expected with the medicinal product.

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.

For information on the management of overdose (in non-emergency situations), contact the Poison Information Centre on 131 126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

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

5.1 Pharmacodynamic Properties

Mechanism of action

Fiasp is a fast-acting insulin aspart formulation. The primary activity of insulin, including insulin aspart, is the regulation of glucose metabolism. Insulin and its analogues 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.

Fiasp is an insulin aspart formulation in which the addition of nicotinamide (niacinamide; vitamin B_3) results in a faster initial absorption of insulin, leading to an earlier onset of action and greater early glucose-lowering effect compared to NovoRapid®. The onset of action was 5 minutes faster and time to maximum glucose infusion rate was 11 minutes earlier with Fiasp than with NovoRapid. The glucose lowering effect (AUC_{GIR}) was 74% larger during the first 30 minutes with Fiasp than with NovoRapid. The total glucose lowering effect over the mealtime phase 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 similar to NovoRapid.

The duration of action was shorter and the late glucose lowering effect was 10% smaller for Fiasp compared to that of NovoRapid. Fiasp injected at the start of a meal produced a significantly greater postmeal glucose lowering effect after a standardised mixed meal test (80 g carbohydrate; 'Ensure®' liquid shake) compared to NovoRapid. The treatment difference in reduction of 2-hour postmeal glucose increment was statistically significant in favour of Fiasp (-0.67 mmol/L $[-1.29; -0.04]_{95\%CI}$). The treatment difference in reduction of 1-hour postmeal glucose increment was -1.18 mmol/L $[-1.65; -0.71]_{95\%CI}$) consistent with the earlier absorption profile (see Table 1, in 'Clinical Trials' and Figure 1).

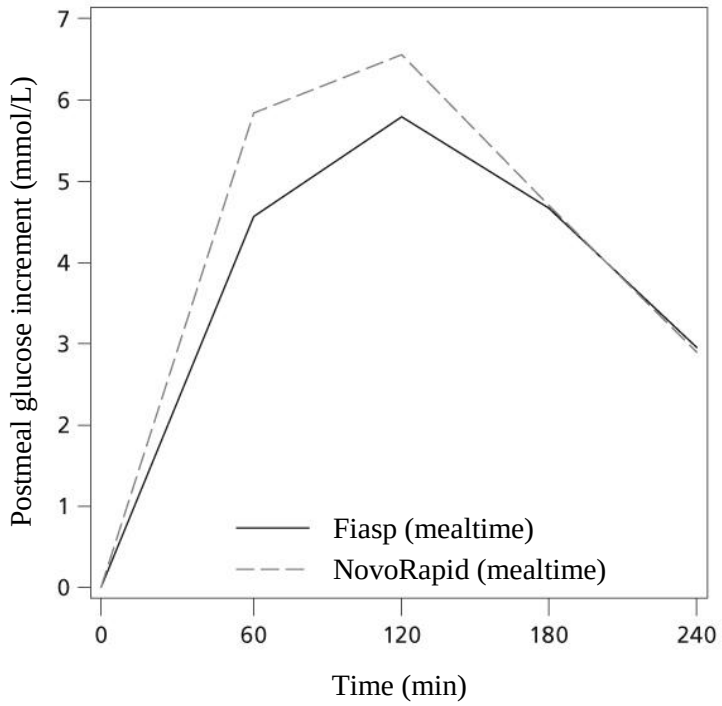


Figure 1 Postmeal glucose increment (meal test) after 26 weeks of treatment in type 1 diabetic patients

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%).

Continuous Subcutaneous Insulin Infusion (CSII)
Fiasp showed a greater postmeal glucose lowering effect after a standardised meal test with regard to 1-hour and 2-hour PPG 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 (Figure 2) in a CSII setting.

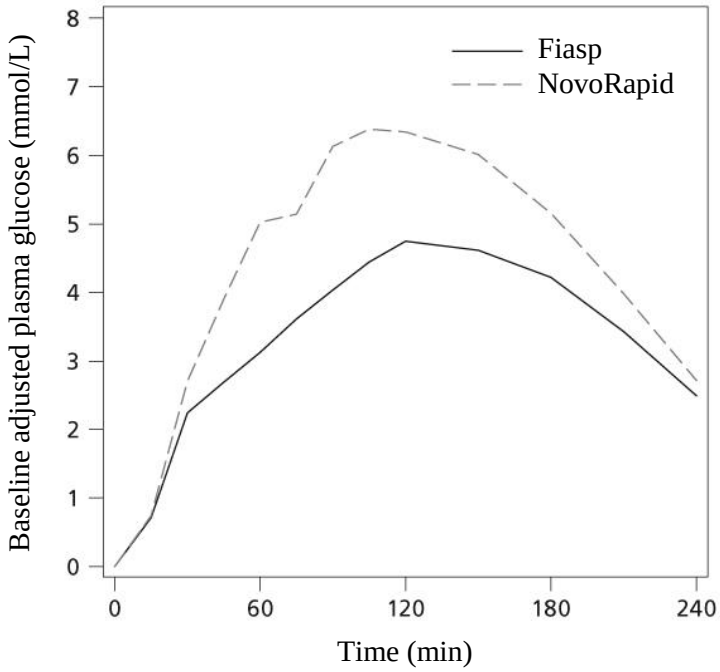


Figure 2 Meal test profiles – mean baseline adjusted plasma glucose profiles in type 1 diabetic patients in a CSII setting

Elderly

In elderly patients with type 1 diabetes, Fiasp showed an earlier onset of action and a greater early glucose lowering effect whilst maintaining a similar total and maximum glucose-lowering effect compared to NovoRapid. The total and the maximum glucose-lowering effect with Fiasp were comparable between elderly and younger adults.

Obesity

The effect of BMI on the pharmacodynamics of Fiasp was explored in a cross-trial analysis of pharmacodynamic studies. Fiasp had a greater early glucose-lowering effect whilst maintaining a total and maximum glucose-lowering effect comparable to NovoRapid across BMI levels in patients with type 1 diabetes.

A trend for decrease in glucose-lowering effect of Fiasp with increasing BMI was observed in patients with type 1 diabetes.

Paediatric population

For children, the glucose-lowering effect of Fiasp at 1 and 2 hours was > 30% greater than with NovoRapid, measured by mean changes in plasma glucose at 1 and 2 hours. There is no clinically relevant difference in the pharmacodynamic properties of Fiasp between children (6-11 years), adolescents (12-18 years) and adult patients with type 1 diabetes.

Clinical trials

Clinical efficacy and safety data

Fiasp has been studied in 2068 randomised adult patients with type 1 diabetes mellitus (1143 patients) and type 2 diabetes mellitus (925 patients) in 3 long-term (18 - 26 weeks of treatment) efficacy and safety trials. Furthermore, Fiasp has been studied in 777 randomised adolescents and children aged 1 to less than 18 years with type 1 diabetes mellitus in a long-term (26 weeks of treatment) efficacy and safety trial.

Patients with type 1 diabetes mellitus
A 26-week active-controlled confirmatory trial was conducted to compare the efficacy and safety of mealtime Fiasp with mealtime NovoRapid, and postmeal Fiasp with mealtime NovoRapid. Subjects were randomised in a 1:1:1 ratio to receive mealtime Fiasp, postmeal Fiasp or mealtime NovoRapid, in combination with once or twice daily insulin detemir. Mealtime Fiasp and NovoRapid were injected 0-2 minutes before the meal, and postmeal Fiasp was injected 20 minutes after the start of the meal. The mean age of the randomised subjects was 44.4 years and mean duration of diabetes was 19.9 years. 58.8% were male. 93.3% were White, 2.3% Black or African American and 6.9% were Hispanic. The mean BMI was 26.7 kg/m^2. The reduction in HbA_{1c} was statistically significantly greater with Fiasp administrated 0-2 minutes before a meal compared to NovoRapid. Fiasp administered 20 minutes after a meal achieved similar HbA_{1c} reduction as NovoRapid dosed at mealtime (Figure 3, Table 1).

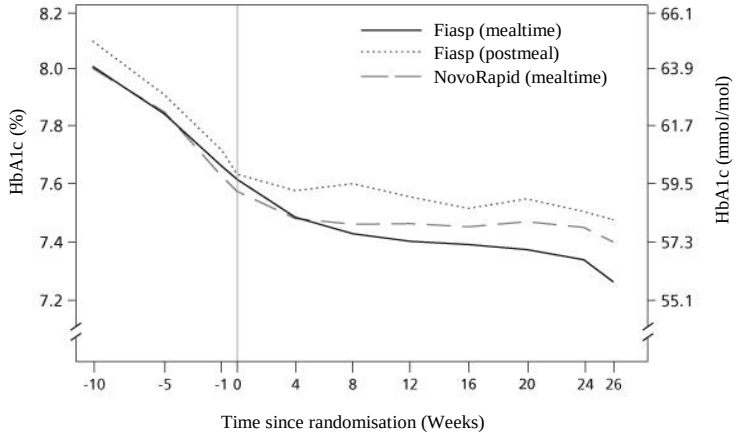


Figure 2 Mean HbA_{1c} in % by treatment week in patients with type 1 diabetes mellitus

In patients with type 1 diabetes, Fiasp provided greater overall glycaemic control than NovoRapid. Fiasp provided better postmeal glycaemic control than NovoRapid with no overall increased risk of severe or blood glucose confirmed hypoglycaemia in patients with type 1 or type 2 diabetes mellitus (Tables 3 and 4).

Patients with type 2 diabetes mellitus
A 26-week active-controlled confirmatory trial was conducted to compare the efficacy and safety of mealtime Fiasp (N= 345) with mealtime NovoRapid (N=344) in bolus naïve subjects with type 2 diabetes. Both treatments were in combination with insulin glargine and metformin in a basal bolus regimen. Fiasp or NovoRapid was injected 0-2 minutes before the meal. The mean age of the randomised subjects was 59.5 years and mean duration of diabetes was 12.7 years. 48.8% were male. 81.0% were White, 5.8% Black or African American and 6.4% were Hispanic. The mean BMI was 31.2 kg/m^2. In patients with type 2 diabetes mellitus, Fiasp was non-inferior to NovoRapid (met the pre-specified non-inferiority margin (0.4%)) in achieving glycaemic control (Table 4).

Fiasp as add-on to once daily basal insulin with metformin resulted in a superior reduction in HbA_{1c} and a statistically significant reduction in postmeal glucose in patients with type 2 diabetes mellitus compared to once daily basal insulin with metformin (Table 5).

Table 3 Results from 26 week basal-bolus clinical trial in adults 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]*[DF]	*0.04 [-0.04;0.12]*[E]	
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]*[DF]	*0.47[-0.41;1.36]*[E]	
Patients (%) achieving HbA_{1c} < 7%			
All patients	33.3	23.3	28.2
Estimated odds ratio	*1.47 [1.02;2.13]*[DF]	*0.73 [0.49;1.07]*[E]	
2-hour postmeal glucose increment (mmol/L)[B]			
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]*[DF]	*0.30 [-0.34;0.93]*[E]	
1-hour postmeal glucose increment (mmol/L)[B]			
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]*[DF]	*0.93[0.46;1.40]*[E]	
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
Estimated treatment difference	*0.12 [-0.30;0.55]*[D]	*0.16 [-0.27;0.58]*[E]	
Observed rate of severe or BG confirmed hypoglycaemia[C] **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]*[D]	*0.92 [0.81;1.06]*[E]	
Total bolus insulin dose (unit/kg/day)			
Baseline → End of trial	0.33[A]→ 0.39[A]	0.35[A] → 0.39[A]	0.36[A] → 0.38[A]
Total basal insulin dose (unit/kg/day)			
Baseline → End of trial	0.41[A] → 0.39[A]	0.43[A] → 0.42[A]	0.43[A] → 0.43[A]

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

[B] Meal test (blood samples drawn 2 mins before meal, and at 1 hr, 2 hr, 3 hr and 4 hr time points post-meal)

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

[D] The difference is for Fiasp mealtime – NovoRapid mealtime

[E] The difference is for Fiasp postmeal – NovoRapid mealtime

[F] Statistically significant in favour of Fiasp mealtime

Table 4 Results from 26 week basal-bolus clinical trial in adults 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]*	
Patients (%) achieving HbA_{1c} < 7%			
All patients	74.8		75.9
Estimated odds ratio		*1.01 [0.70;1.44]*	
2-hour postmeal glucose increment (mmol/L)[B]			
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)[B]			
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]*[D]	
Bodyweight (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[C] 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]*	
Total bolus insulin dose (unit/kg/day)			
Baseline → End of trial	0.21[A] → 0.49[A]		0.21[A] → 0.51[A]
Total basal insulin dose (unit/kg/day)			
Baseline → End of trial	0.56[A] → 0.53[A]		0.52[A] → 0.48[A]

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

[B] Meal test

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

[D] Statistically significant in favour of Fiasp

Table 5 Results from 18 week basal-bolus vs. basal clinical trial in adults with type 2 diabetes

	Fiasp + basal insulin[A] + metformin	basal insulin[A] + metformin
N	116	120
HbA_{1c} (%)		
Baseline → End of trial	7.9 → 6.8	7.9 → 7.7
Adjusted change from baseline	- 1.16	-0.22
Estimated treatment difference	*-0.94 [-1.17; -0.72][B]*	
HbA_{1c} (mmol/mol)		
Baseline → End of trial	63.2 → 50.7	63.1 → 60.7
Adjusted change from baseline	-12.72	-2.43
Estimated treatment difference	*-10.29 [-12.75; -7.82][B]*	

Baseline, End of trial values are based on the mean of the observed last available values. The 95% confidence interval is stated in '[]'
[A] Basal insulin: insulin glargine, insulin detemir or NPH
[B] statistically significant in favour of Fiasp

Elderly
In the three controlled clinical studies, 192 of 1219 (16%) Fiasp treated patients with type 1 diabetes mellitus or type 2 diabetes mellitus were ≥ 65 years of age and 24 of 1219 (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. Fiasp was effective in controlling blood glucose levels as assessed by several measures of intermediate and long-term glycaemic control, such as HbA_{1c}, serum fructosamine, and 1,5-AG, and measures related to postprandial glucose control, such as 2-hour post-prandial glucose (PPG) increment (self-monitored plasma glucose, SMPG) and mean of 9-point SMPG profile. There were two patients from the Fiasp group who each reported two treatment-emergent infusion site reactions.

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 mellitus 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 1–5 years, 100 children aged 6–11 years and 144 adolescents aged 12–17 years. Patients in the Fiasp postmeal arm included 16 children aged 1–5 years, 100 children aged 6–11 years and 143 adolescents aged 12–17 years.

Fiasp was shown to be effective in terms of glycaemic control with regards to change in HbA_{1c}, both when administered postmeal (ETD: 0.13 % $[-0.01; 0.26]_{95\% CI}$) and at mealtime (ETD: -0.17 % $[-0.30; -0.03]_{95\% CI}$), compared to NovoRapid. In particular Fiasp mealtime showed superior glycaemic control compared to NovoRapid mealtime.

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

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

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

Table 6 Results from a 26 week basal-bolus clinical trial in children and adolescents with type 1 diabetes

	Fiasp mealtime + insulin degludec	Fiasp postmeal + insulin degludec	NovoRapid mealtime + insulin degludec
N	260	259	258
HbA_{1c} (%)			
Baseline → End of trial	7.6 → 7.6	7.6 → 7.9	7.5 → 7.8
Adjusted change from baseline	0.06	0.35	0.22
Estimated treatment difference	*-0.17 [-0.30; -0.03]*[A,C]	*0.13 [-0.01; 0.26]*[B]	
HbA_{1c} (mmol/mol)			
Baseline → End of trial	59.3 → 59.9	59.4 → 63.0	58.8 → 61.3
Adjusted change from baseline	0.62	3.84	2.44
Estimated treatment difference	*-1.82 [-3.08; -0.36]*[A,C]	*1.40 [-0.06; 2.86]*[B]	
1-hour postmeal glucose increment mean over all three main meals (SMPG) (mmol/L)			
Baseline → End of trial	1.2 → 0.3	1.0 → 1.6	1.0 → 1.1
Adjusted change from baseline	-0.79	0.57	0.14
Estimated treatment difference	*-0.93 [-1.35; -0.52]*[AC]	*0.43 [0.02; 0.85]*[B]	
Observed rate of severe or BG confirmed* hypoglycaemia per patient year of exposure (percentage of patients)	27.9 (87.4)	28.2 (88.0)	25.7 (84.1)
Estimated rate ratio	*1.11 [0.90; 1.37]*[A]	*1.11 [0.90; 1.37]*[B]	
Observed rate of severe or BG confirmed* nocturnal hypoglycaemia per patient year of exposure (percentage of patients)	3.1 (42.9)	3.7 (48.4)	2.5 (40.3)
Estimated rate ratio	*1.29 [0.93; 1.79]*[A]	*1.50 [1.09; 2.08]*[B]	

Baseline, End of trial values are based on the mean of the observed last available values. The 95% confidence interval is stated in '[]'
*Severe according to the ISPAD 2014 classification and/or have a recorded plasma glucose < 3.1 mmol/L
[A] The difference is for Fiasp mealtime – NovoRapid mealtime
[B] The difference is for Fiasp postmeal – NovoRapid mealtime
[C] Statistically significant in favour of Fiasp mealtime

5.2 Pharmacokinetic Properties

Absorption

Human insulin molecules self-associate to form hexamers. The substitution of proline by aspartic acid at position B28 in insulin aspart produces an intermolecular repulsion which reduces the tendency of the insulin molecules to self-associate. The inclusion of nicotinamide in the Fiasp formulation further reduces self-association. This increases the rate of dissociation of hexamers into dimers and monomers in the subcutaneous layer. This results in a faster initial absorption of insulin, leading to an earlier onset of exposure and greater early insulin exposure following bolus administration via subcutaneous injection (Figure 4) or through CSII in pumps (Figure 4) compared to NovoRapid.

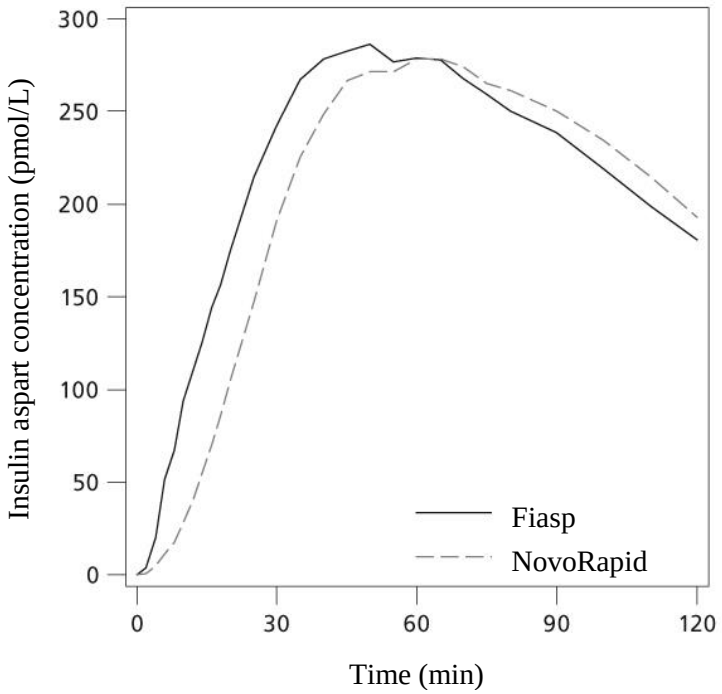


Figure 3 Meal insulin profile in patients with type 1 diabetes after subcutaneous injection: 0-2 hours

After administration of Fiasp, insulin appeared in the circulation approximately 4 minutes after administration (Figure 3). 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. The total insulin exposure ($AUC_{insulin\ aspart,\ 0\text{-}12hours}$) and the maximum insulin concentration (C_{max}) were comparable between Fiasp and NovoRapid. Total exposure and maximum insulin concentration increases proportionally with increasing subcutaneous dose of Fiasp within the therapeutic dose range.

The pharmacokinetic profiles of Fiasp and NovoRapid are distinct during the first hour following administration which is of particular importance for a mealtime insulin. The earlier onset of action of Fiasp and the subsequent increased glucose lowering effect compared with NovoRapid must be considered when prescribing Fiasp.

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 5).

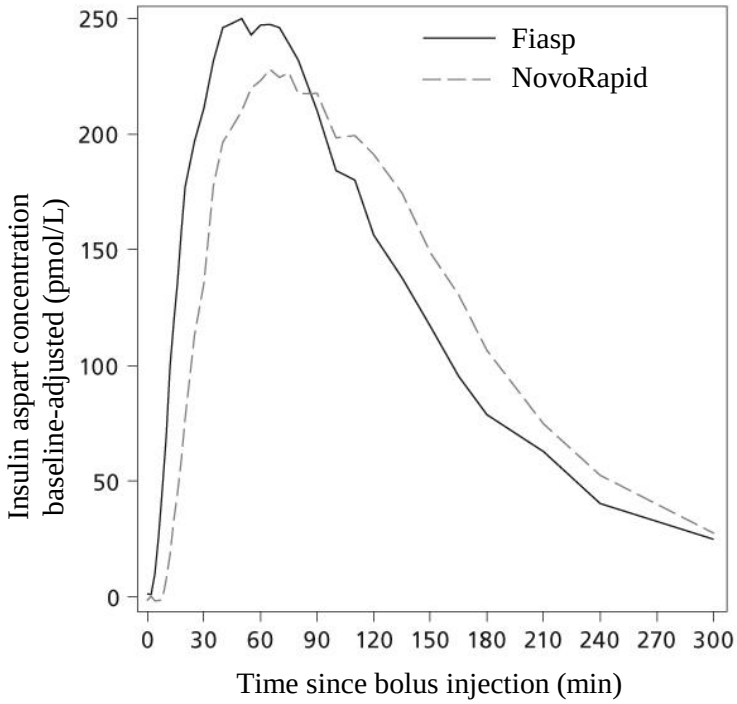


Figure 4 Mean insulin profiles in patients with type 1 diabetes in a CSII setting (0–5 hours) corrected for basal insulin infusion

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

Metabolism
Degradation of insulin aspart is similar to that of human insulin.

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

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.
The effect of age on the total insulin exposure of Fiasp was based on results from a population pharmacokinetic analysis in patients with type 1 diabetes. No relationship between total insulin exposure of Fiasp and age was observed (age range from 18-83).

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

The effect of BMI on the total insulin exposure of Fiasp was based on results from a population pharmacokinetic analysis in patients with type 1 diabetes. No relationship between total insulin exposure of Fiasp and BMI was observed.

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

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.

5.3 Preclinical Safety Data

Genotoxicity
Insulin aspart did not cause gene mutations, chromosomal damage or DNA damage in a range of genotoxicity tests.

Carcinogenicity
Lifetime carcinogenicity studies of insulin aspart have not been performed in animals. In 52-week repeat dose toxicity studies in Sprague-Dawley rats at doses up to 50 U/kg/d SC, the only significant toxicity findings were related to hypoglycaemia. At a higher dose of 200

U/kg/d SC in female Sprague-Dawley rats, insulin aspart, like human insulin, caused induction of mammary tumours. The clinical relevance of these findings is not known. Neither clinical nor epidemiological studies conducted to date have shown an association between insulin use and carcinogenesis but the available evidence is considered too limited to be conclusive at this time. *In vitro* studies showed that the mitogenic activity of insulin aspart does not differ from that observed with human insulin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Phenol
Metacresol
Glycerol
Zinc
Dibasic sodium phosphate dihydrate
Arginine
Nicotinamide (niacinamide; vitamin B3)
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to Fiasp may cause degradation of insulin aspart. Fiasp must not be diluted or mixed with any other products except infusion fluids as described in method of administration.

6.3 Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Before first use:
Store in a refrigerator (2°C – 8°C). Keep away from the freezing element. Do not freeze. **Fiasp FlexTouch:** Keep the cap on the pen in order to protect from light. **Fiasp vial and Fiasp Penfill:** Keep the vial/cartridge in the carton in order to protect from light.

After first opening or carried as a spare:
Fiasp FlexTouch: 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. After first opening, the product may be stored for a maximum of 4 weeks.
Fiasp vial: Do not store above 30°C. Can be stored in the refrigerator (2°C – 8°C). Do not freeze. Keep the vial in the carton in order to protect from light. After first opening, the product may be stored for a maximum of 4 weeks (including time in a pump reservoir). Fiasp may be used in an infusion pump (CSII) for a maximum of 6 days.
Fiasp Penfill: Do not refrigerate. Do not store above 30°C. Do not freeze. If cartridge is carried as a spare and unused, the cartridge should be kept in the carton in order to protect from light. After first opening, the product may be stored for a maximum of 4 weeks.

6.5 Nature and Contents of Container

Fiasp FlexTouch: 3 mL solution in 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. Pack sizes of:

- 1 pre-filled pen
- 5 pre-filled pens

Fiasp vial: 10 mL solution in vial (type 1 glass) closed with a halobutyl/polyisoprene rubber disc and a protective tamper-proof plastic cap in a carton. Pack size of:

- 1 vial

Fiasp vials are for use with insulin syringes with the corresponding unit scale and for use in CSII. Fiasp may be used in an infusion pump (CSII) as described in 'Dosage and Administration.' Tubings in which the inner surface materials are made of polyethylene have been evaluated and found compatible with pump use.

Fiasp Penfill: 3 mL solution in cartridge (type 1 glass), with a plunger (halobutyl) and a stopper (halobutyl/polyisoprene) in a carton. Pack size of:

- 5 cartridges

*Not all presentations and pack sizes may be marketed.

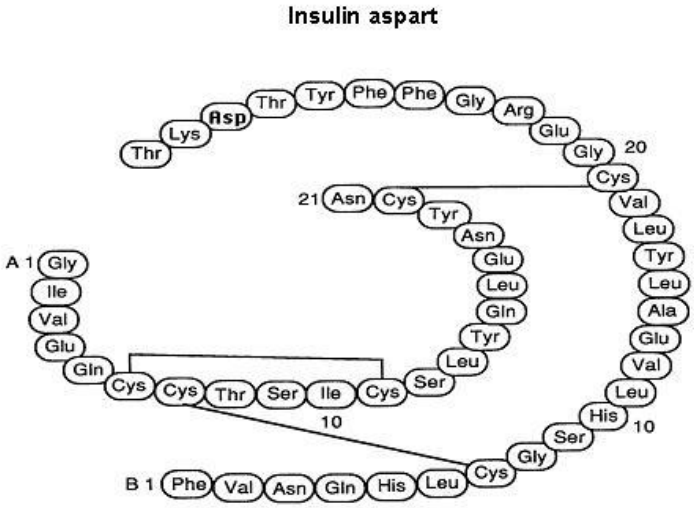
6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Chemical structure

Insulin aspart (rys) has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.



CAS number

116094-23-6

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4

8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Limited
Level 10, 118 Mount Street
North Sydney NSW 2060

Website: www.novonordisk.com.au

9. DATE OF FIRST APPROVAL

27 July 2017

10. DATE OF REVISION

20 December 2021

Summary table of changes

Section changed	Summary of new information
All	Updated to align with TGA Approved PI format
6.3	Reduction of infusion pump reservoir in-use shelf life from 9 to 6 days.
	Inclusion of the Black Triangle symbol and its associated text
4.1, 4.2, 4.4, 4.8, 5.1	Inclusion of data and statements to reflect use in paediatric patients
4.8	Updated adverse effects
4.2, 4.4, 4.8	Addition of cutaneous amyloidosis warning and recommendation around use to reduce or prevent listed skin and subcutaneous tissue disorder reactions through injection site rotation.
8	Update to sponsor address