Fiasp®
insulin aspart injection 100 units/mL

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FIASP® safely and effectively. See full prescribing information for FIASP®.

FIASP® (insulin aspart injection) for subcutaneous or intravenous use
Initial U.S. Approval: 2000

——— INDICATIONS AND USAGE ———

- FIASP® is a rapid-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus (1).

———DOSAGE AND ADMINISTRATION———

- Individualize and adjust the dosage of FIASP® based on route of administration, individual's metabolic needs, blood glucose monitoring results and glycemic control goal (2.2).
- Dosage adjustments may be needed when switching from another insulin, with changes in physical activity, changes in concomitant medications, changes in meal patterns, changes in renal or hepatic function or during acute illness (2.2).
- *Subcutaneous injection (2.2):*
  - Inject at the start of a meal or within 20 minutes after starting a meal into the abdomen, upper arm, or thigh.
  - Rotate injection sites within the same region.
  - Should generally be used in regimens with an intermediate- or long-acting insulin.
- *Intravenous Infusion:* Administer only under medical supervision after diluting to concentrations from 0. 5 to 1 unit/mL insulin aspart in infusion systems using polypropylene infusion bags (2.2).

——— DOSAGE FORMS AND STRENGTHS ———

Injection: 100 units/mL (U-100):

- 10 mL multiple-dose vial (3)
- 3 mL single-patient-use FIASP® FlexTouch® pen (3)

——— CONTRAINDICATIONS ———

- During episodes of hypoglycemia (4).
- Hypersensitivity to insulin aspart or one of the excipients in FIASP® (4).

——— WARNINGS AND PRECAUTIONS ———

- *Never share* a FIASP® FlexTouch® pen between patients, even if the needle is changed (5.1).
- *Hyper- or hypoglycemia with changes in insulin regimen:* Carry out under close medical supervision and increase frequency of blood glucose monitoring (5.2).
- *Hypoglycemia:* May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness (5.3).
- *Hypoglycemia due to medication errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection (5.4).
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated (5.5).
- *Hypersensitivity reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue FIASP®, monitor and treat if indicated (5.6).
- *Fluid retention and heart failure with concomitant use of thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs (5.7).

——— ADVERSE REACTIONS ———

Adverse reactions observed with FIASP® include: hypoglycemia, allergic reactions, hypersensitivity, injection site reactions, lipodystrophy, and weight gain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

——— DRUG INTERACTIONS ———

- *Drugs that Increase Hypoglycemia Risk or Increase or Decrease Blood Glucose Lowering Effect:* Adjustment of dosage may be needed; closely monitor blood glucose (7).
- *Drugs that Blunt Hypoglycemia Signs and Symptoms (e.g., beta-blockers, clonidine, guanethidine, and reserpine):* Increased frequency of glucose monitoring may be required (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

New: 09/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FIASP® is indicated to improve glycemic control in adults with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always check insulin label before administration *[see Warnings and Precautions (5.4)]*.
- Inspect visually for particulate matter and discoloration. Only use FIASP® if the solution appears clear and colorless.
- Train patients on proper use and injection technique before initiating FIASP®.
- DO NOT administer FIASP® intramuscularly.
- DO NOT dilute or mix FIASP® with any other insulin products or solutions, except infusion fluids.

2.2 General Dosing Instructions

- Individualize the dosage of FIASP® based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal.
- Dose adjustments may be needed when switching from another insulin, with changes in physical activity, changes in concomitant medications, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia *[see Warnings and Precautions (5.2, 5.3) and Drug Interactions (7)]*.

Subcutaneous Injection:

- Inject FIASP® at the start of a meal or within 20 minutes after starting a meal subcutaneously into the abdomen, upper arm, or thigh.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions (6.1)]*.
- FIASP® given by subcutaneous injection should generally be used in regimens with intermediate or long-acting insulin *[see Warnings and Precautions (5.2)]*.
- Instruct patients on basal-bolus treatment who forget a mealtime dose to monitor their blood glucose level to decide if an insulin dose is needed, and to resume their usual dosing schedule at the next meal.

Intravenous Administration:

- Administer FIASP® intravenously only under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.5)]*.
- Dilute FIASP® to concentrations from 0.5 unit/mL to 1 unit/mL insulin aspart in infusion systems using polypropylene infusion bags.
- FIASP® is stable at room temperature for 24 hours in 0.9% sodium chloride or 5% dextrose infusion fluids *[see How Supplied/Storage and Handling (16.2)]*

2.3 Converting to FIASP® from Other Insulins in Patients with Either Type 1 or Type 2 Diabetes

If converting from another mealtime insulin to FIASP®, the change can be done on a unit-to-unit basis *[see Clinical Studies (14)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 units of insulin aspart per mL (U-100) is available as a clear and colorless solution in:

- 10 mL multiple-dose vial
- 3 mL single-patient-use FIASP® FlexTouch® pen

4 CONTRAINDICATIONS

FIASP® is contraindicated

- During episodes of hypoglycemia *[see Warnings and Precautions (5.3)]*.
- In patients with known hypersensitivity to insulin aspart or one of the excipients in FIASP®. *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a FIASP® FlexTouch® Pen Between Patients

FIASP® FlexTouch® disposable prefilled pen should never be shared between patients, even if the needle is changed. Patients using FIASP® vials should never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin, insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under close medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, dosage adjustments in concomitant oral anti-diabetic treatment may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of all insulin therapies, including FIASP® *[see Adverse Reactions (6.1)]*. Severe hypoglycemia can cause seizures, may lead to unconsciousness, may be life-threatening, or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g. driving or operating other machinery). FIASP®, or any insulin, should not be used during episodes of hypoglycemia *[see Contraindications (4)]*.

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) *[see Drug Interactions (7)]*, or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. As with all insulin preparations, the glucose lowering effect time course of FIASP® may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature *[see Clinical Pharmacology (12.2)]*.

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication *[see Drug Interactions (7)]*. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia *[see Use in Specific Populations (8.6, 8.7)]*.

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between insulin products have been reported. To avoid medication errors between FIASP® and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypokalemia

All insulin products, including FIASP®, can cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to potassium concentrations).

5.6 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including FIASP® *[see Adverse Reactions (6.1)]*. If hypersensitivity reactions occur, discontinue FIASP®; treat per standard of care and monitor until symptoms and signs resolve. FIASP® is contraindicated in patients who have had hypersensitivity reactions to insulin aspart, or one of the excipients in FIASP® *[see Contraindications (4)]*.

5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-Gamma Agonists

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including FIASP®, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Hypokalemia *[see Warnings and Precautions (5.5)]*
- Hypersensitivity and allergic reactions *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates actually observed in clinical practice.

The data in Table 1 reflect the exposure of 763 patients with type 1 diabetes to FIASP® in one clinical trial with a mean exposure duration of 25 weeks *[see Clinical Studies (14)]*. The mean age was 44.4 years and the mean duration of diabetes was 19.9 years. 59% were male, 93% were Caucasian, 2% were Black or African American and 7% were Hispanic. The mean BMI was 26.7 kg/m^2 and the mean HbA_{1c} at baseline was 7.6%.

The data in Table 2 reflect the exposure of 341 patients with type 2 diabetes to FIASP® in one clinical trial with a mean exposure duration of 24 weeks *[see Clinical Studies (14)]*. The mean age was 59.6 years and the mean duration of diabetes was 13.2 years. 47% were male, 80% were Caucasian, 6% were Black or African American and 8% were Hispanic. The mean BMI was 31.5 kg/m^2 and the mean HbA_{1c} at baseline was 8.0%.

Common adverse reactions, excluding hypoglycemia, were defined as events occurring in ≥5% and occurring at the same rate or greater for FIASP®-treated subjects than comparator-treated subjects.

Table 1. Adverse Reactions (%*) in Patients with Type 1 Diabetes

	Mealtime FIASP® + Insulin detemir (N=386)	Postmeal FIASP® + Insulin detemir (N=377)
Nasopharyngitis	20.2	23.9
Upper respiratory tract infection	9.1	7.4
Nausea	4.9	5.0
Diarrhea	5.4	3.2
Back pain	5.2	4.0

*Incidence ≥ 5% and occurring at the same rate or greater with FIASP® than comparator

Table 2. Adverse Reactions (%*) in Patients with Type 2 Diabetes

	FIASP® + Insulin glargine (N=341)
Urinary tract infection	5.9

*Incidence ≥ 5% and occurring at the same rate or greater with FIASP® than comparator

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including FIASP® *[see Warnings and Precautions (5.3)]*. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for FIASP® with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that occur in clinical practice.

Incidence rates for severe hypoglycemia in adults with type 1 and type 2 diabetes mellitus treated with FIASP® in clinical trials are shown in Table 3 *[see Clinical Studies (14)]*.

Table 3. Proportion (%) of Patients with Type 1 Diabetes and Type 2 Diabetes Experiencing at Least One Episode of Severe Hypoglycemia in Adult Clinical Trials

	Study A (Type 1)		Study B (Type 2)
	Mealtime FIASP® + Insulin detemir (N=386)	Postmeal FIASP® + Insulin detemir (N=377)	FIASP® + Insulin glargine (N=341)
Severe hypoglycemia*	6.7	8.0	3.2

*Severe hypoglycemia: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including FIASP®, and may be life threatening *[see Warnings and Precautions (5.6)]*. In the clinical program, generalized hypersensitivity reactions (manifested by generalized skin rash and facial edema) was reported in 0.4% of patients treated with FIASP®. Allergic skin manifestations reported with FIASP® in 1.7% of patients from the clinical program include eczema, rash, rash pruritic, urticaria and dermatitis.

Lipodystrophy

Administration of insulin, including FIASP®, has resulted in lipohypertrophy (enlargement or thickening of tissue) and lipoatrophy (depression in the skin). In the clinical program, lipodystrophy was reported in 0.4% of patients treated with FIASP® *[see Dosage and Administration (2.2)]*.

Injection Site Reactions

As with other insulin therapy, patients may experience rash, redness, inflammation, bruising or itching at the site of FIASP® injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of FIASP®. In the clinical program, injection site reactions occurred in 1.6% of patients treated with FIASP®. In Study A, patients with type 1 diabetes treated with FIASP® reported 2.2% injection site reactions.

Weight Gain

Weight gain can occur with insulin therapy, including FIASP®, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria. In Study A, patients with type 1 diabetes treated with FIASP® gained an average of 0.7 kg and in Study B, patients with type 2 diabetes treated with FIASP® gained an average of 2.7 kg.

Peripheral Edema

Insulin, including FIASP®, may cause sodium retention and edema, particularly if previous poor metabolic control is improved by intensified insulin therapy. In the clinical program, peripheral edema occurred in 0.8% of patients treated with FIASP®.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to FIASP® in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In a 26-week study in adult subjects with type 1 diabetes (Study A *[see Clinical Studies (14)]*), among the 763 subjects who received FIASP®, 97.2% were positive for cross-reacting anti-insulin antibodies (AIA) at least once during the study, including 90.3% that were positive at baseline. A total of 24.8% of patients who received FIASP® were positive for anti-drug (insulin aspart) antibodies (ADA) at least once during the study, including 17.3% that were positive at baseline.

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with FIASP®.

Table 4. Clinically Significant Drug Interactions with FIASP®

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.
Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when FIASP® is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of FIASP®	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dose increases and increased frequency of glucose monitoring may be required when FIASP® is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of FIASP®	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when FIASP® is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine.
Intervention:	Increased frequency of glucose monitoring may be required when FIASP® is co-administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with FIASP® in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. Available information from published randomized controlled trials with insulin aspart use during the second trimester of pregnancy have not reported an association with insulin aspart and major birth defects or adverse maternal or fetal outcomes *[see Data]*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal reproduction studies, administration of subcutaneous insulin aspart to pregnant rats and rabbits during the period of organogenesis did not cause adverse developmental effects at exposures 8- times and equal to the human subcutaneous dose of 1.0 unit/kg/day, respectively. Pre- and post-implantation losses and visceral/skeletal abnormalities were seen at higher exposures, which are considered secondary to maternal hypoglycemia. These effects were similar to those observed in rats administered regular human insulin *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA_{1c} >7% and has been reported to be as high as 20-25% in women with a HbA_{1c} >10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Human Data

Published data from 5 randomized controlled trials of 441 pregnant women with diabetes mellitus treated with insulin aspart starting during the late 2nd trimester of pregnancy did not identify an association of insulin aspart with major birth defects or adverse maternal or fetal outcomes. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including a variable duration of treatment and small size of the majority of the trials.

Animal Data

Fertility, embryo-fetal and pre-and postnatal development studies have been performed with insulin aspart and regular human insulin in rats and rabbits. In a combined fertility and embryo-fetal development study in rats, insulin aspart was administered before mating, during mating, and throughout pregnancy. Further, in a pre- and postnatal development study insulin aspart was given throughout pregnancy and during lactation to rats. In an embryo-fetal development study insulin aspart was given to female rabbits during organogenesis. The effects of insulin aspart did not differ from those observed with subcutaneous regular human insulin. Insulin aspart, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 units/kg/day (approximately 32 times the human subcutaneous dose of 1.0 unit/kg/day, based on human exposure equivalents) and in rabbits at a dose of 10 units/kg/day (approximately three times the human subcutaneous dose of 1.0 unit/kg/day, based on human exposure equivalents). No significant effects were observed in rats at a dose of 50 units/kg/day and in rabbits at a dose of 3 units/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 unit/kg/day for rats and equal to the human subcutaneous dose of 1.0 unit/kg/day for rabbits, based on human exposure equivalents. The effects are considered secondary to maternal hypoglycemia.

8.2 Lactation

Risk Summary

There are no data on the presence of FIASP® in human milk, the effects on the breastfed infant, or the effect on milk production. One small published study reported that exogenous insulin, including insulin aspart, was present in human milk. However, there is insufficient information to determine the effects of insulin aspart on the breastfed infant and no available information on the effects of insulin aspart on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for insulin, any potential adverse effects on the breastfed child from FIASP® or insulin aspart or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of FIASP® in pediatric patients have not been established.

8.5 Geriatric Use

In the three controlled clinical studies, 192 of 1219 (16%) FIASP® treated patients with type 1 or type 2 diabetes 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 these elderly patients and younger adult patients.

Nevertheless, caution should be exercised when FIASP® is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia *[see Warnings and Precautions (5.3), Adverse Reactions (6.1) and Clinical Studies (14)]*.

Pharmacokinetic/pharmacodynamic study to assess the effect of age on the onset of FIASP® action has been performed *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent FIASP® dose adjustment and more frequent blood glucose monitoring *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent FIASP® dose adjustment and more frequent blood glucose monitoring *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.5)]*. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

11 DESCRIPTION

FIASP® (insulin aspart injection) is a rapid-acting insulin analog for subcutaneous or intravenous administration used to lower blood glucose. Insulin aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8 daltons.

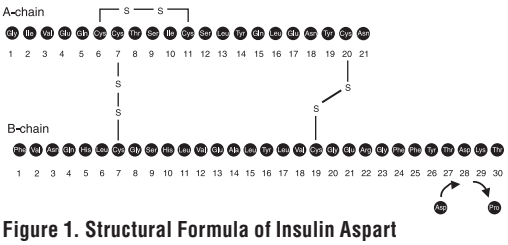

Figure 1. Structural Formula of Insulin Aspart

FIASP® is an aqueous, sterile, clear and colorless solution that contains insulin aspart 100 units/mL, glycerol, phenol, metacresol, zinc, disodium phosphate dihydrate, arginine hydrochloride, niacinamide (vitamin B_3), and water for injections. FIASP® has a pH of 7.1. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

The time course of insulin action (i.e., glucose lowering) may vary considerably in different individuals or within the same individual. The average pharmacodynamic profile [i.e., glucose lowering effect measured as glucose infusion rate (GIR) in a euglycemic clamp study] for subcutaneous administration of 0.1, 0.2, and 0.4 unit/kg of FIASP® in 46 patients with Type 1 diabetes is shown in Figure 2 and key characteristics of the timing of the effect are described in Table 5 below.

Table 5. Timing of insulin effect (i.e., mean pharmacodynamic effect) after subcutaneous administration of 0.1, 0.2 and 0.4 unit/kg of FIASP® in patients (N=46) with Type 1 Diabetes and corresponding to the data shown in Figure 2

Parameter for Insulin Effect	FIASP® 0.1 unit/kg	FIASP® 0.2 unit/kg	FIASP® 0.4 unit/kg
Time to first measurable effect	~20 minutes	~17 minutes	~16 minutes
Time to peak effect	~91 minutes	~122 minutes	~133 minutes
Time for effect to return to baseline	~5 hours	~6 hours	~7 hours

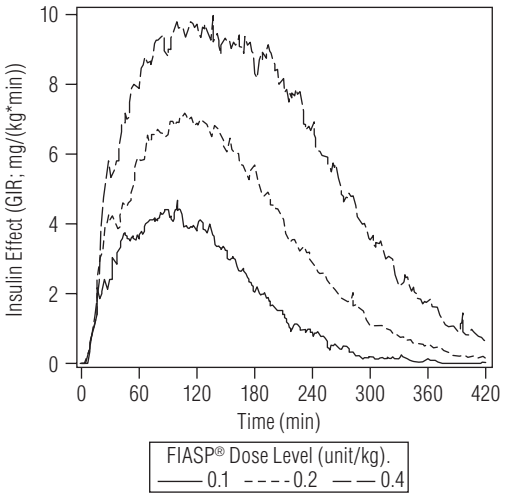

Figure 2. Mean insulin effect (i.e., mean pharmacodynamic effect) over time after subcutaneous administration of 0.1, 0.2 and 0.4 unit/kg of FIASP® in patients (N=46) with Type 1 diabetes

On average, the pharmacodynamic effects of FIASP®, measured as area under the glucose infusion rate-time curve (AUC_{GIR}), was 697 mg/kg, 1406 mg/kg, and 2427 mg/kg following administration of 0.1, 0.2, and 0.4 unit/kg of FIASP®.

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

12.3 Pharmacokinetics

Absorption

Pharmacokinetic results from a euglycemic clamp study in adult patients with type 1 diabetes (N=51) showed that insulin aspart appeared in the circulation ~2.5 minutes after administration of FIASP® (Figure 3). Time to maximum insulin concentrations was achieved ~63 minutes after administration of FIASP®.

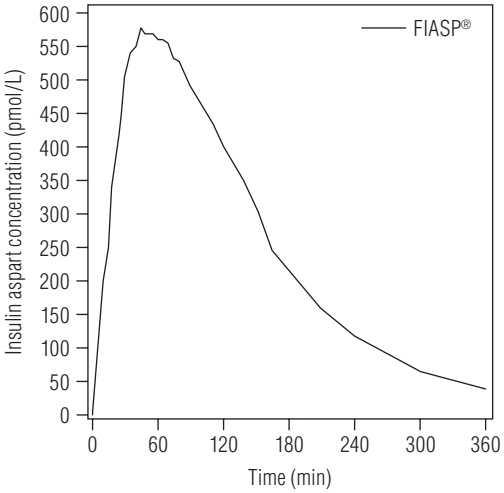

Figure 3. Mean Insulin Aspart Serum Concentration Profile in Adult Subjects with Type 1 Diabetes (N=51) following a single 0.2 unit/kg dose (subcutaneous) of FIASP®

Total insulin exposure and maximum insulin concentration increase proportionally with increasing subcutaneous dose of FIASP® within the therapeutic dose range.

Distribution

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

Elimination

The apparent terminal half-life after subcutaneous administration of FIASP® is about 1.1 hours.

Specific Populations

Age (18 to ≥65 years), gender, BMI, and race did not meaningfully affect the pharmacokinetics and pharmacodynamics of FIASP®.

Pregnant Women

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of FIASP® has not been studied *[see Use in Specific Populations (8.1)]*.

Patients with Renal and Hepatic Impairment

Based on studies conducted with insulin aspart, renal and hepatic impairment is not known to impact the pharmacokinetics of insulin aspart.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with insulin aspart at 10, 50, and 200 units/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 units/kg/day, based on units/body surface area, respectively). At a dose of 200 units/kg/day, insulin aspart increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for insulin aspart was not significantly different than for regular human insulin. The relevance of these findings to humans is not known.

Insulin aspart was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, *in vivo* micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes.

In fertility studies in male and female rats, at subcutaneous doses up to 200 units/kg/day (approximately 32 times the human subcutaneous dose, based on units/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

The efficacy of FIASP® was evaluated in 3 randomized, active-controlled trials of 18 to 26 weeks duration. In total 1224 adult subjects were randomized to FIASP® (N=763 with type 1 diabetes; N=461 with type 2 diabetes). In adult patients with type 1 diabetes, mealtime FIASP® and postmeal FIASP® led to non-inferior glycemic control compared to mealtime NovoLog®, both in combination with insulin detemir. In adult patients with type 2 diabetes, mealtime FIASP® provided non-inferior glycemic control compared to mealtime NovoLog®, both in combination with metformin. In addition, mealtime FIASP® in a basal-bolus regimen with metformin also provided statistically significant improvement in the overall glycemic control compared to basal insulin therapy alone with metformin in adult patients with type 2 diabetes.

14.2 Type 1 Diabetes - Adults

Study A (NCT01831765): FIASP® added to insulin detemir in patients with Type 1 DM inadequately controlled at baseline.

The efficacy of FIASP® was evaluated in a 26-week, randomized, active controlled, treat-to-target, multicenter trial in 1143 adult patients with type 1 diabetes inadequately controlled at baseline. Patients were randomized to either blinded mealtime FIASP® (N=381), blinded mealtime NovoLog® (N=380), or open-label postmeal FIASP® (N=382), all in combination with once or twice daily insulin detemir. At randomization, patients were switched to FIASP® on a unit to unit basis. Mealtime FIASP® or NovoLog® was injected 0-2 minutes before the meal, and postmeal FIASP® was injected 20 minutes after the start of the meal.

The mean age of the randomized subjects was 44.4 years and mean duration of diabetes was 19.9 years. 59% were male, 93% were White, 2% were Black or African American, and 7% were Hispanic. The mean BMI was 26.7 kg/m^2.

After 26 weeks of treatment, treatment difference in HbA_{1c} reduction from baseline between mealtime FIASP® compared to mealtime NovoLog®, and the treatment difference between postmeal FIASP® compared to mealtime NovoLog® met the pre-specified non-inferiority margin (0.4%). See Table 6. Insulin doses were similar among study arms at baseline and at the end of the trial.

Table 6. Results from Study A: 26-Week Trial of Mealtime FIASP® and Postmeal FIASP® compared to Mealtime NovoLog® Used in Combination with Insulin Detemir in Adults with Type 1 Diabetes

	Mealtime FIASP® + insulin detemir	Postmeal FIASP® + insulin detemir	Mealtime NovoLog® + insulin detemir
Number of subjects randomized (N)	381	382	380
HbA_{1c} (%)			
Baseline (mean)	7.6	7.6	7.6
Adjusted mean change from baseline	-0.32	-0.13	-0.17
Estimated treatment difference vs. mealtime NovoLog® [95% CI]*	-0.15 [-0.23;-0.07]		
Estimated treatment difference vs. mealtime NovoLog® [95% CI]*		0.04 [-0.04;0.12]	

Baseline is based on the mean of the observed last available values prior to randomization.

*Tested for non-inferiority

7.6% of subjects on the Mealtime FIASP® arm, 7.6% of subjects on the Postmeal FIASP® arm, and 5.3% of subjects on the Mealtime NovoLog® arm were missing the final HbA_{1c} assessment.

14.3 Type 2 Diabetes - Adults

Study B (NCT01819129): FIASP® added to basal insulin and oral antidiabetics in patients with Type 2 DM inadequately controlled at baseline on basal insulin and oral antidiabetics

The efficacy of FIASP® was evaluated in a 26-week randomized, double-blind, active controlled, treat-to-target, multicenter, multinational, parallel group trial in 689 adult patients with type 2 diabetes who were inadequately controlled at baseline on basal insulin and oral antidiabetic therapy and had been on these therapies for at least 6 months. Patients were randomized to either mealtime FIASP® or to mealtime NovoLog®, both in combination with insulin glargine and metformin in a basal-bolus regimen. Mealtime FIASP® or mealtime NovoLog® was injected 0-2 minutes before the meal.

The mean age of the randomized subjects was 59.5 years and the mean duration of diabetes was 12.7 years. 49% were male, 81% were White, 6% were Black or African American, and 6% were Hispanic. The mean BMI was 31.2 kg/m^2.

After 26 weeks of treatment, the treatment difference in HbA_{1c} reduction from baseline between mealtime FIASP® and mealtime NovoLog®, both in combination with insulin glargine and metformin, met the pre-specified non-inferiority margin (0.4%). See Table 7. Insulin doses were similar among study arms at the end of the trial.

Table 7. Results from Study B: 26-Week Trial of Mealtime FIASP® Compared to Mealtime NovoLog®, Both used in Combination with Insulin Glargine and Metformin, in Adults with Type 2 Diabetes

	Mealtime FIASP® +insulin glargine +metformin	Mealtime NovoLog® +insulin glargine +metformin
Number of subjects randomized (N)	**345**	**344**
HbA_{1c} (%)		
Baseline	8.0	7.9
Adjusted change from baseline	-1.38	-1.36
Estimated treatment difference vs. NovoLog® [95%CI]*	-0.02 [-0.15;0.10]	

Baseline is based on the mean of the observed last available values prior to randomization.

*Tested for non-inferiority

11.9% of subjects on the Mealtime FIASP® arm and 10.2% of subjects on the Mealtime NovoLog® arm were missing the final HbA_{1c} assessment.

Study C (NCT01850615): FIASP® added to basal insulin and metformin in patients with Type 2 DM inadequately controlled at baseline on basal insulin and metformin

The efficacy of FIASP® was evaluated in an 18-week randomized, open-label, parallel group trial in 236 adult patients with type 2 diabetes who were inadequately controlled on basal insulin and metformin therapy, either with or without other oral antidiabetic therapy, for at least 3 months. Patients were randomized to either mealtime FIASP® in addition to basal insulin and metformin or to continuing basal insulin and metformin therapy without FIASP®. The basal insulins used in both treatment arms were insulin glargine, insulin detemir or NPH. All patients were also required to be on ≥1000 mg metformin treatment at baseline.

The mean age of the trial population was 57.4 years and the mean duration of diabetes was 11.3 years. 48% were male, 70% were White, 4% were Black or African American, and 37% were Hispanic. The mean BMI was 30.8 kg/m^2.

After 18 weeks of treatment, addition of FIASP® to basal insulin and metformin statistically significantly reduced HbA_{1c} compared to continuing basal insulin and metformin therapy without addition of FIASP® (Table 8).

Table 8. Results from Study C: 18-Week Trial of Mealtime FIASP® in Adults with Type 2 Diabetes Inadequately Controlled at Baseline on Basal Insulin and Metformin

	FIASP® + basal insulin + metformin	Basal insulin + metformin
Number of subjects randomized (N)	**116**	**120**
HbA_{1c} (%)		
Baseline	7.9	7.9
Adjusted change from baseline	-1.16	-0.22
Estimated treatment difference vs. basal insulin+metformin [95%CI]	-0.94 [-1.17; -0.72]*	
Proportion of patients Achieving HbA_{1c} < 7% at Trial End	60.3%	18.3%

Baseline is based on the mean of the observed last available values prior to randomization.

*p<0.0001, 1-sided p-value evaluated at 2.5% level for superiority.

6.0% of subjects on the mealtime FIASP® arm and 3.3% of subjects on the placebo arm were missing the final HbA_{1c} assessment.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FIASP® (insulin aspart injection) 100 units of insulin aspart per mL (U-100) is available as a clear and colorless solution in:

10 mL multiple-dose vials	NDC 0169-3201-11
3 mL single-patient use FIASP® FlexTouch® pen	NDC 0169-3204-15

16.2 Recommended Storage

Unused FIASP® vials should be stored between 2° to 8°C (36° to 46°F) in a refrigerator, but not in or near a freezing compartment. FIASP® should not be exposed to excessive heat or light and must never be frozen. **Do not freeze FIASP® and do not use FIASP® if it has been frozen.** FIASP® should not be drawn into a syringe and stored for later use. Only use the product if it has a clear and almost colorless appearance.

Keep the cap on the pen in order to protect from light. Keep unused vials and FIASP® FlexTouch® in the carton so they will stay clean and protected from light.

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

The storage conditions for vials and FIASP® FlexTouch® pens are summarized in Table 9:

Table 9. Storage Conditions for Vial and FIASP® FlexTouch®

FIASP® presentation	Not in-use (unopened)		In-use (opened)	
	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)
10 mL vial	28 days	Until expiration date	28 days	28 days
3 mL FIASP® FlexTouch®	28 days	Until expiration date	28 days	28 days

Storage of FIASP® in Intravenous Infusion Fluids:

Infusion bags prepared as indicated under *Dosage and Administration (2.2)* are stable at room temperature for 24 hours.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved Patient Labeling (Patient Information and Instructions for Use).

Never Share a FIASP® FlexTouch® Pen Device Between Patients

Advise patients that they should never share a FIASP® FlexTouch® pen device with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens. Advise patients using FIASP® vials not to share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens *[see Warnings and Precautions (5.1)]*.

Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of FIASP® therapy. Instruct patients on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals. Instruct patients on the management of hypoglycemia *[see Warnings and Precautions (5.3)]*.

Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions have occurred with FIASP®. Inform patients on the symptoms of hypersensitivity reactions *[see Warnings and Precautions (5.6)]*.

Hypoglycemia due to Medication Errors

Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products.

Women of Reproductive Potential

Advise patients to inform their health care professional if they are pregnant or are contemplating pregnancy.

Administration

FIASP® must only be used if the solution is clear and colorless with no particles visible. Patients must be advised that FIASP® must NOT be diluted or mixed with any other insulin or solution *[see Dosage and Administration (2.1)]*.

Instruct patients on basal-bolus treatment who forget a mealtime dose to monitor their blood glucose level to decide if an insulin dose is needed, and to resume their usual dosing schedule at the next meal.

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Version: 1

PATENT Information: http://novonordisk-us.com/patients/products/product-patents.html

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

For information about FIASP® contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, New Jersey 08536
1-800-727-6500
www.novonordisk-us.com

USA17INS03320 October 2017

novo nordisk®

Patient Information
FIASP® (fee' asp)
(insulin aspart injection)
for subcutaneous or intravenous use

Do not share your FIASP® with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

What is FIASP®?

- FIASP® is a man-made insulin that is used to control high blood sugar in adults with diabetes mellitus.
- It is not known if FIASP® is safe and effective in children.

Who should not take FIASP®?

Do not take FIASP® if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to insulin aspart or any of the ingredients in FIASP®.

Before taking FIASP®, tell your healthcare provider about all your medical conditions including, if you:

- have kidney problems.
- have liver problems.
- are pregnant or plan to become pregnant. Talk with your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if FIASP® passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while using FIASP®.
- are taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

Before you start taking FIASP®, talk to your healthcare provider about low blood sugar and how to manage it.

How should I take FIASP®?

- **Read the Instructions for Use** that come with your FIASP®.
- Take FIASP® exactly as your healthcare provider tells you to.
- **FIASP® starts acting fast.** You should take your dose of FIASP® at the beginning of the meal or within 20 minutes after starting a meal.
- Know the type and strength of insulin you take. **Do not** change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- If you miss a dose of FIASP®, monitor your blood sugar levels to decide if an insulin dose is needed. Continue with your regular dosing schedule at the next meal.
- **Check your blood sugar levels**. Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- **Do not reuse or share needles with other people. You may give other people a serious infection or get a serious infection from them.**

What should I avoid while taking FIASP®?

While taking FIASP® do not:

- Drive or operate heavy machinery until you know how FIASP® affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of FIASP®?

FIASP® may cause serious side effects that can lead to death, including:

- **low blood sugar (hypoglycemia).** Signs and symptoms that may indicate low blood sugar include:
  - dizziness or light-headedness
  - anxiety, irritability, or mood changes
  - slurred speech
  - confusion
  - headache
  - blurred vision
  - sweating
  - hunger
  - shakiness
  - fast heart beat

Your insulin dose may need to change because of:

- change in level of physical activity or exercise
- change in diet
- weight gain or loss
- increased stress
- illness

- **low potassium in your blood (hypokalemia).**
- **serious allergic reactions (whole body reactions).** Get emergency medical help right away, if you have any of these signs or symptoms of a severe allergic reaction:
  - a rash over your whole body, trouble breathing, a fast heartbeat, swelling of your face, tongue or throat, sweating, extreme drowsiness, dizziness, confusion.
- **heart failure.** Taking certain diabetes pills called TZDs (thiazolidinediones) with FIASP® may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with FIASP®. Your healthcare provider should monitor you closely while you are taking TZDs with FIASP®. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:
  - Shortness of breath, swelling of your ankles or feet, sudden weight gain.

Treatment with TZDs and FIASP® may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

Common side effects of FIASP® may include:

- skin problems such as eczema, rash, itching, redness and swelling of your skin (dermatitis)
- reactions at the injection site such as itching, rash
- skin thickening or pits at the injection site (lipodystrophy)
- weight gain

These are not all the possible side effects of FIASP®. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of FIASP®.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about FIASP® that is written for health professionals. Do not use FIASP® for a condition for which it was not prescribed. Do not give FIASP® to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in FIASP®?

Active Ingredient: insulin aspart

Inactive Ingredients: glycerol, phenol, metacresol, zinc, disodium phosphate dihydrate, arginine hydrochloride, niacinamide and water for injections

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration.
Revised: 09/2017

novo nordisk®

Instructions for Use

FIASP® (fee' asp) FlexTouch® Pen
(insulin aspart injection)

- **Do not** share your FIASP® FlexTouch® Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.
- **FIASP® FlexTouch® Pen ("Pen") is a prefilled disposable pen** containing 300 units of U-100 FIASP® (insulin aspart injection). You can inject from 1 to 80 units in a single injection. The units can be increased by 1 unit at a time.
- This Pen is **not recommended** for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.
- **Do not** use a syringe to remove FIASP® from the FlexTouch® Pen.

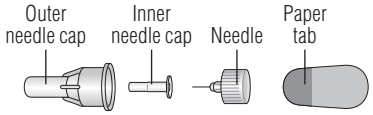
Supplies you will need to give your FIASP® injection:

- FIASP® FlexTouch® Pen
- a new NovoFine®, NovoFine® Plus or NovoTwist® needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. **See "After your injection" at the end of these instructions.**

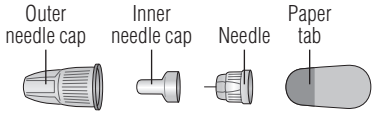
Preparing your FIASP® FlexTouch® Pen:

- Wash your hands with soap and water.
- Before you start to prepare your injection, check the FIASP® FlexTouch® Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.
- FIASP® should look clear and colorless. **Do not** use FIASP® if it is thick, cloudy, or is colored.
- **Do not** use FIASP® past the expiration date printed on the label or 28 days after you start using the Pen.
- **Always** use a new needle for each injection to help ensure sterility and prevent blocked needles. **Do not** reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.

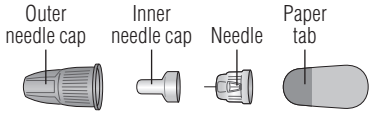
NovoFine®

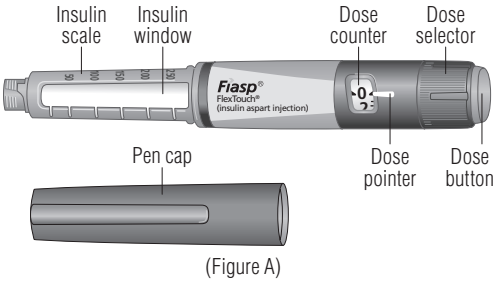


NovoFine® Plus



NovoTwist®

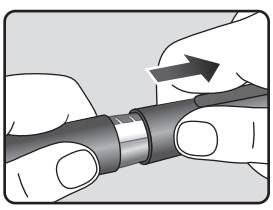




(Figure A)

Step 1:

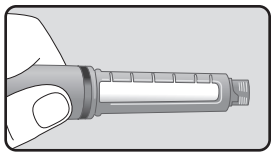
- Pull Pen cap straight off (See Figure B).



(Figure B)

Step 2:

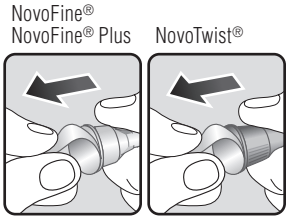
- **Check the liquid in the Pen** (See Figure C). FIASP® should look clear and colorless. **Do not** use it if it looks cloudy or colored.



(Figure C)

Step 3:

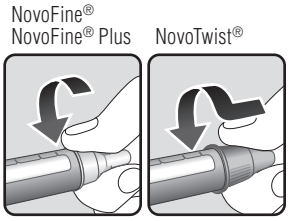
- **Select a new needle.**
- Pull off the paper tab from the outer needle cap (See Figure D).



(Figure D)

Step 4:

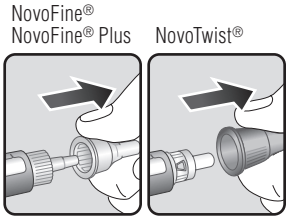
- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).



(Figure E)

Step 5:

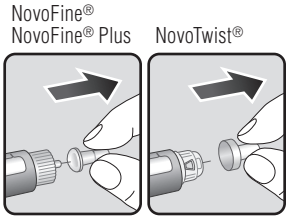
- Pull off the outer needle cap. **Do not** throw it away (See Figure F).



(Figure F)

Step 6:

- Pull off the inner needle cap and throw it away (See Figure G).

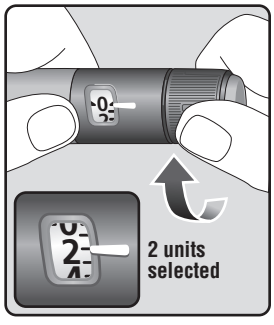


(Figure G)

Priming your FIASP® FlexTouch® Pen:

Step 7:

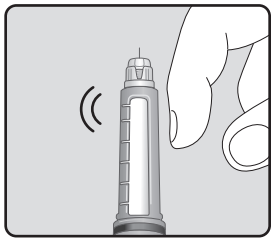
- Turn the dose selector to **select 2 units** (See Figure H).



(Figure H)

Step 8:

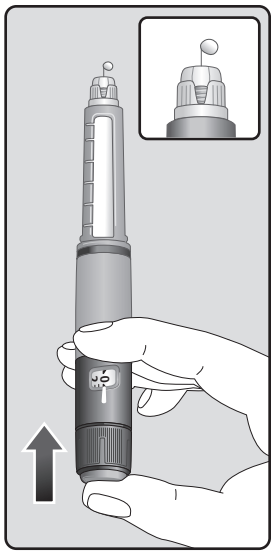
- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).



(Figure I)

Step 9:

- **Hold the Pen with the needle pointing up.** Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.
- A drop of insulin should be seen at the needle tip (See Figure J).
  - If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
  - If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.



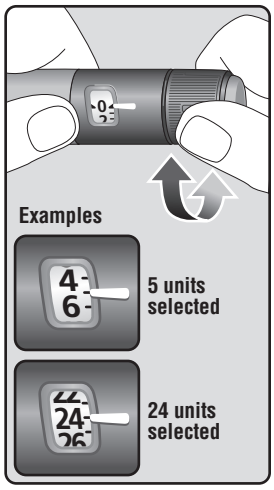
(Figure J)

Selecting your dose:

Step 10:

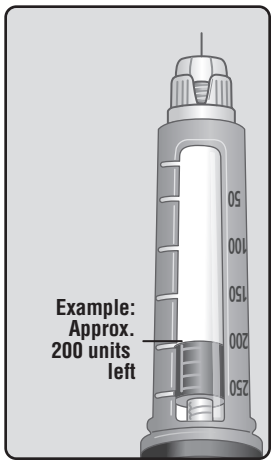
Check to make sure the dose selector is set at 0.

- **Turn the dose selector to select the number of units you need to inject.** The dose pointer should line up with your dose (See Figure K).
  - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  - The **even** numbers are printed on the dial.
  - The **odd** numbers are shown as lines.



(Figure K)

- The FIASP® FlexTouch® Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).



(Figure L)

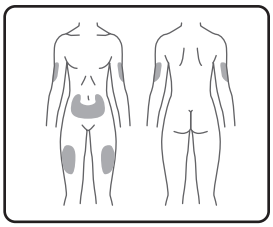
- **To see how much insulin is left in your FIASP® FlexTouch® Pen:**
  - Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are **at least 80** units left in your Pen.
  - If the dose counter shows **less than 80**, the number shown in the dose counter is the number of units left in your Pen.

Giving your injection:

- Inject your FIASP® exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- You should take your dose of FIASP® at the start of a meal or within 20 minutes after starting a meal.
- FIASP® can be injected under the skin (subcutaneously) of your stomach area (abdomen), upper legs (thighs) or upper arms. **Do not** inject FIASP® into your muscle.
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

Step 11:

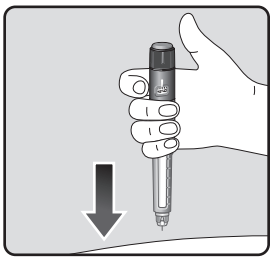
- Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure M).



(Figure M)

Step 12:

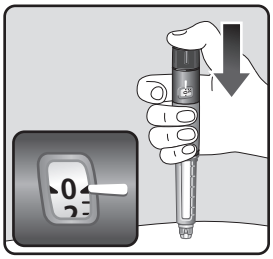
- **Insert the needle into your skin** (See Figure N).
  - **Make sure you can see the dose counter. Do not** cover it with your fingers; this can stop your injection.



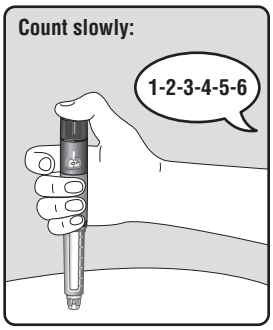
(Figure N)

Step 13:

- **Press and hold down the dose button until the dose counter shows "0"** (See Figure O).
  - The "0" must line up with the dose pointer. You may then hear or feel a click.
- **Keep the needle in your skin after** the dose counter has returned to "0" and **slowly count to 6** (See Figure P).
  - **When the dose counter returns to "0", you will not get your full dose until 6 seconds later.**
  - **If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.**
  - **If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.**



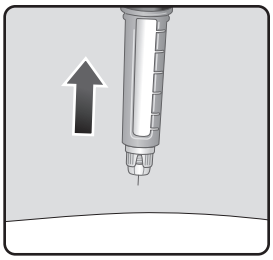
(Figure O)



(Figure P)

Step 14:

- **Pull the needle out of your skin** (See Figure Q).
  - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.

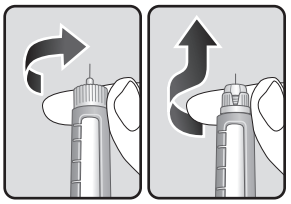


(Figure Q)

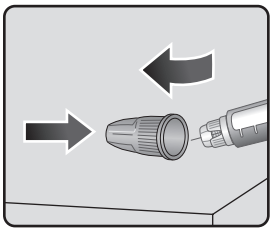
Step 15:

- **Carefully remove the needle from the Pen and throw it away** (See Figure R).
  - **Do not** recap the needle. Recapping the needle can lead to needle stick injury.
- If you **do not** have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.
  - **Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

NovoFine®
NovoFine® Plus NovoTwist®



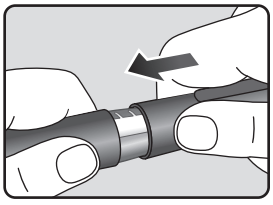
(Figure R)



(Figure S)

Step 16:

- Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

After your injection:

- Put your used FIASP® FlexTouch® Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share needles or syringes with another person. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store my FIASP® FlexTouch® Pen?

Before use:

- Store unused FIASP® FlexTouch® Pens in the refrigerator at 36°F to 46°F (2°C to 8°C) or at room temperature below 86°F (30°C).
- **Do not** freeze FIASP®. **Do not** use FIASP® if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.
- If FIASP® FlexTouch® Pens are stored at room temperature prior to first use, it should be used or thrown away within 28 days.

Pen in use:

- Store the Pen you are currently using without the needle attached at room temperature below 86°F (30°C) or in the refrigerator at 36°F to 46°F (2°C to 8°C) for up to 28 days.
- Keep FIASP® away from excessive heat or light.
- The FIASP® FlexTouch® Pen you are using is to be thrown away after 28 days, even if it still has insulin left in it and the expiration date has not passed.

General Information about the safe and effective use of FIASP®

- **Keep FIASP® FlexTouch® Pens and needles out of the reach of children.**
- **Always** use a new needle for each injection.
- **Do not** share FIASP® FlexTouch® Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

Revised: 09/2017

For more information go to www.FIASPflextouch.com

USA17INS03320 October 2017

novo nordisk®

Instructions for Use

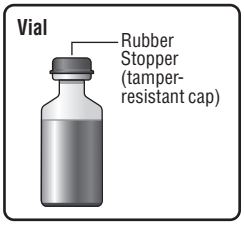
FIASP® (fee' asp)
(insulin aspart injection)
10 mL vial (100 units/mL, U-100)

Read this Instructions for Use before you start taking FIASP® and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment. The vial is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product and insulin syringe.

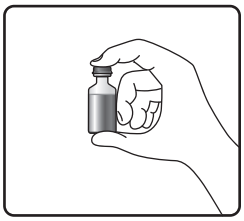
Do not reuse or share syringes or needles with other people. You may give other people a serious infection or get a serious infection from them.

Supplies you will need to give your FIASP® injection:

- a 10 mL FIASP® vial
- a U-100 insulin syringe and needle
- 2 alcohol swabs
- 1 sharps container for throwing away used needles and syringes. See "Disposing of your used needles and syringes" at the end of these instructions.



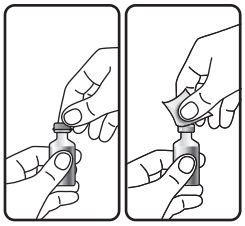
Preparing your FIASP® dose:



- **Do not** roll or shake the FIASP® vial. Shaking the FIASP® vial right before the dose is drawn into the syringe may cause bubbles or foam. This can cause you to draw up the wrong dose of insulin.
- The tamper-resistant cap should not be loose or damaged before the first use. **Do not** use if the tamper-resistant cap is loose or damaged before using FIASP® for the first time.
- Wash your hands with soap and water.
- **Before you start to prepare your injection, check the FIASP® label to make sure that you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.**
- Check that the FIASP® vial is not cracked or damaged. **Do not** use if the FIASP® vial is cracked or damaged.
- FIASP® should look clear and colorless. **Do not** use FIASP® if it is thick, cloudy, or is colored.
- **Do not** use FIASP® past the expiration date printed on the label.

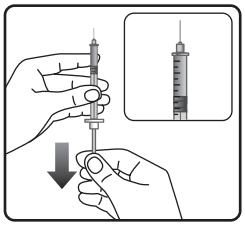
Step 1: Pull off the tamper-resistant cap (See Figure A).

Step 2: Wipe the rubber stopper with an alcohol swab (See Figure B).



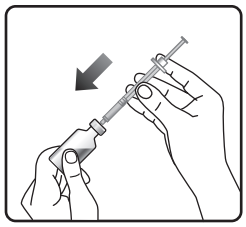
(Figure A Figure B)

Step 3: Hold the syringe with the needle pointing up. Pull down on the plunger until the tip of the plunger reaches the line for the number of units for your prescribed dose (See Figure C).



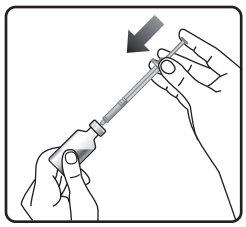
(Figure C)

Step 4: Push the needle through the rubber stopper of the FIASP® vial (See Figure D).



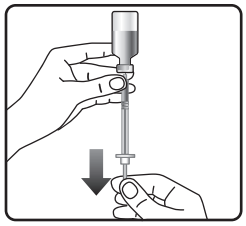
(Figure D)

Step 5: Push the plunger all the way in. This puts air into the FIASP® vial (See Figure E).



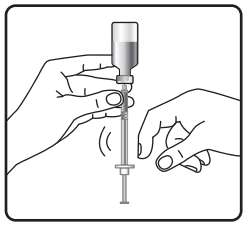
(Figure E)

Step 6: Turn the FIASP® vial and syringe upside down and slowly pull the plunger down until the tip of the plunger is a few units past the line for your dose (See Figure F).



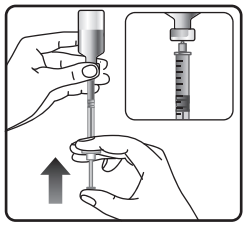
(Figure F)

If there are air bubbles, tap the syringe gently a few times to let any air bubbles rise to the top (See Figure G).



(Figure G)

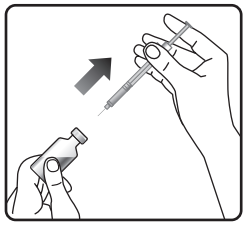
Step 7: Slowly push the plunger up until the tip of the plunger reaches the line for your prescribed FIASP® dose (See Figure H).



(Figure H)

Step 8: Check the syringe to make sure you have the right dose of FIASP®.

Step 9: Pull the syringe out of the rubber stopper on the vial (See Figure I).

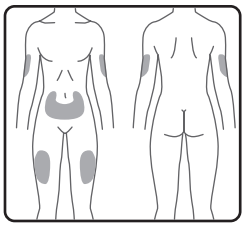


(Figure I)

Giving your FIASP® injection:

- Inject your FIASP® exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- You should take your dose of FIASP® at the start of a meal or within 20 minutes after starting a meal.
- FIASP® can be injected under the skin (subcutaneously) of your stomach area, upper legs, or upper arms. **Do not** inject FIASP® into your muscle.
- Change (rotate) your injection site for each injection. **Do not** use the same injection site for each injection.
- **Do not** dilute or mix FIASP® with any other type of insulin products or solutions.

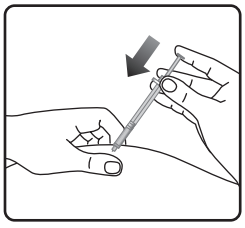
Step 10: Choose your injection site and wipe the skin with an alcohol swab (See Figure J). Let the injection site dry before you inject your dose.



(Figure J)

Step 11: Insert the needle into your skin. Push down on the plunger to inject your dose (See Figure K).

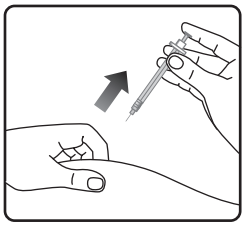
Make sure you have injected all the insulin in the syringe.



(Figure K)

Step 12: Pull the needle out of your skin. After your injection you may see a drop of FIASP® at the needle tip. This is normal and does not affect the dose you just received (See Figure L).

- If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.



(Figure L)

After your injection:

- **Do not** recap the needle. Recapping the needle can lead to needle stick injury.

Disposing of your used needles and syringes:

Put your used insulin needles and syringes in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and syringes in your household trash.

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic;
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out;
- upright and stable during use;
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share needles or syringes with another person. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store FIASP®?

- **Do not** freeze FIASP®. **Do not** use FIASP® if it has been frozen.
- Keep FIASP® away from excessive heat or light.
- Store unopened FIASP® vials in the refrigerator at 36°F to 46°F (2°C to 8°C) or at room temperature below 86°F (30°C).
- Store opened FIASP® vials in the refrigerator at 36°F to 46°F (2°C to 8°C) or at room temperature below 86°F (30°C).
- Unopened FIASP® vials may be used until the expiration date printed on the label, if they are kept in the refrigerator.
- If FIASP® vials are stored at room temperature prior to first use, they should be used or thrown away within 28 days.
- Opened FIASP® vials should be thrown away after 28 days, even if they still have insulin left in them.

General information about the safe and effective use of FIASP®

- Always use a new syringe and needle for each injection to help ensure sterility and prevent blocked needles.
- **Do not** reuse or share syringes or needles with other people. You may give other people a serious infection or get a serious infection from them.
- Keep FIASP® vials, syringes, and needles out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

PATENT Information: http://novonordisk-us.com/patients/products/product-patents.html

For information about FIASP® contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, New Jersey 08536
1-800-727-6500
www.novonordisk-us.com

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