ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Kixelle 100 units/ml solution for injection in vial
Kixelle 100 units/ml solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 100 units (equivalent to 3.5 mg) insulin aspart*.

Kixelle 100 units/ml solution for injection in vial

Each vial contains 10 ml equivalent to 1,000 units.

Kixelle 100 units/ml solution for injection in pre-filled pen

Each pre-filled pen contains 3 ml equivalent to 300 units.

*produced in *Pichia pastoris* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
The solution is clear, colourless and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kixelle is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

4.2 Posology and method of administration

Posology

The potency of insulin analogues, including insulin aspart, is expressed in units, whereas the potency of human insulin is expressed in international units.

Kixelle dosing is individual and determined in accordance with the needs of the patient. It should normally be used in combination with intermediate-acting or long-acting insulin.

Moreover, Kixelle vial can be used for continuous subcutaneous insulin infusion (CSII) in pump systems.

Kixelle vial can also be used if intravenous administration of insulin aspart, by physicians or other healthcare staff, is applicable.

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

The individual insulin requirement in adults and children is usually between 0.5 and 1.0 unit/kg/day. In a basal-bolus treatment regimen 50-70% of this requirement may be provided by Kixelle and the remainder by intermediate-acting or long-acting insulin.

Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Special populations
Elderly (≥ 65 years old)

Kixelle can be used in elderly patients.
In elderly patients, glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

Renal impairment

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

Hepatic impairment

Hepatic impairment may reduce the patient's insulin requirements.
In patients with hepatic impairment, glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

Paediatric population

Kixelle can be used in children and adolescents aged 1 year and above in preference to soluble human insulin when a rapid onset of action might be beneficial, for example, in the timing of the injections in relation to meals (see sections 5.1 and 5.2).

The safety and efficacy of Kixelle in children below 1 year of age have not been established.
No data are available.

Transfer from other insulin medicinal products
When transferring from other insulin medicinal products, adjustment of the Kixelle dose and the dose of the basal insulin may be necessary. Kixelle has a faster onset and a shorter duration of action than soluble human insulin. When injected subcutaneously into the abdominal wall, the onset of action will occur within 10-20 minutes of injection. The maximum effect is exerted between 1 and 3 hours after the injection. The duration of action is 3 to 5 hours.

Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

Insulin aspart is a rapid-acting insulin analogue.
Kixelle is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see sections 4.4 and 4.8).
Subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites.

Compared to soluble human insulin the faster onset of action of Kixelle is maintained regardless of the injection site. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Due to the faster onset of action, Kixelle should generally be given immediately before a meal. When necessary Kixelle can be given soon after a meal.

Kixelle 100 units/ml solution for injection in vial
Continuous subcutaneous insulin infusion (CSII)

Kixelle may be used for CSII in pump systems suitable for insulin infusion. CSII should be administered in the abdominal wall. Infusion sites should be rotated.

When used with an insulin infusion pump, Kixelle should not be mixed with any other insulin medicinal products.

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

Patients administering Kixelle by CSII must have an alternative insulin delivery method available in case of pump system failure.

Intravenous use

If necessary, Kixelle can be administered intravenously which should be carried out by physicians or other healthcare professionals.

For intravenous use, infusion systems with Kixelle 100 units/ml at concentrations from 0.05 unit/ml to 1.0 unit/ml insulin aspart in the solutions for infusion sodium chloride 9 mg/ml (0.9%), 5% glucose or 10% glucose including 40 mmol/l potassium chloride using polypropylene infusion bags, are stable at room temperature for 24 hours.

Although stable over time, a certain amount of insulin will be initially adsorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during insulin infusion.

Administration with a syringe

Kixelle vials are for use with insulin syringes with the corresponding unit scale. See also section 6.6.

Kixelle 100 units/ml solution for injection in pre-filled pen
Kixelle pre-filled pen is only suitable for subcutaneous injections. If administration by syringe or intravenous injection is necessary, a vial should be used. If administration by infusion pump is necessary, a vial should be used.

Kixelle pre-filled pen delivers insulin in increment of 1 unit up to a maximum single dose of 80 units. Kixelle pre-filled pen is designed to be used with commercially available insulin pen needles. See also section 6.6.

For detailed user instructions, please refer to the package leaflet.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded.

Travel

Before travelling between different time zones, the patient should seek the doctor's advice since this may mean that the patient has to use the insulin and meals at different times.

Hyperglycaemia

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. Usually the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia

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

Especially in children, care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake, physical activities and current blood glucose level in order to minimise the risk of hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. In case of hypoglycaemia or if hypoglycaemia is suspected Kixelle must not be injected. After stabilisation of patient's blood glucose adjustment of the dose should be considered (see sections 4.8 and 4.9).

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

A consequence of the pharmacodynamics of rapid-acting insulin analogues is that if hypoglycaemia occurs, it may occur earlier after an injection when compared with soluble human insulin.

Since Kixelle should be administered in immediate relation to a meal, the rapid onset of action should be considered in patients with concomitant diseases or treatment where a delayed absorption of food might be expected.

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

When patients are transferred between different types of insulin medicinal products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin.

Transfer from other insulin medicinal products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human insulin or human

insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. Patients transferred to Kixelle from another type of insulin may require an increased number of daily injections or a change in dose from that used with their usual insulin medicinal products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Injection site reactions

As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. Continuous rotation of the injection site within a given area reduces the risk of developing these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of Kixelle.

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.

Combination of insulin aspart with pioglitazone

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

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 insulin aspart and other insulin products.

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.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

The following substances may reduce the patient's insulin requirements:
Oral antidiabetic medicinal products, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulphonamides.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Kixelle can be used in pregnancy. Data from two randomised controlled clinical trials (322 and 27 exposed pregnancies) do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to human insulin (see section 5.1).

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 trimester. After delivery, insulin requirements normally return rapidly to pre-pregnancy values.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

Summary of the safety profile

Adverse reactions observed in patients using insulin aspart are mainly due to the pharmacologic effect of insulin.

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control (see section 4.8, Description of selected adverse reactions).

At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Tabulated list of adverse reactions

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA frequency and System Organ Class. Frequency categories are defined according to the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

MedDRA system organ class	**very common**	**uncommon**	**rare**	**very rare**	**Not known**
Immune system disorders		Urticaria, rash, eruptions		Anaphylactic reactions*	
Metabolism and nutritions disorders	Hypoglycaemia*				
Nervous system disorders			Peripheral neuropathy (painful neuropathy)		
Eye disorders		Refraction disorders, diabetic retinopathy			
Skin and subcutaneous tissue disorders		Lipodystrophy *			Cutaneous amyloidosis* †
General disorders and administration site conditions		Injection site reactions, oedema			

*see section 4.8, Description of selected adverse reactions.
† adverse drug reaction (ADR) from postmarketing sources.

Description of selected adverse reactions

Anaphylactic reactions
The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure) is very rare but can potentially be life threatening.

Hypoglycaemia
The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

In clinical trials, the frequency of hypoglycaemia varied with patient population, dose regimens and level of glycaemic control. During clinical trials the overall rates of hypoglycaemia did not differ between patients treated with insulin aspart compared to human insulin.

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

Paediatric population

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in the paediatric population do not indicate any differences to the broader experience in the general population.

Other special populations

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in the elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

Reporting of suspected adverse reactions

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

4.9 Overdose

A specific overdose for insulin cannot be defined, however, hypoglycaemia may develop over sequential stages if too high doses relative to the patient's requirement are administered:

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Kixelle is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Mechanism of action and pharmacodynamic effects

The blood glucose lowering effect of insulin aspart is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

Insulin aspart produces a more rapid onset of action compared to soluble human insulin, together with a lower glucose concentration, as assessed within the first four hours after a meal. Insulin aspart has a shorter duration of action compared to soluble human insulin after subcutaneous injection.

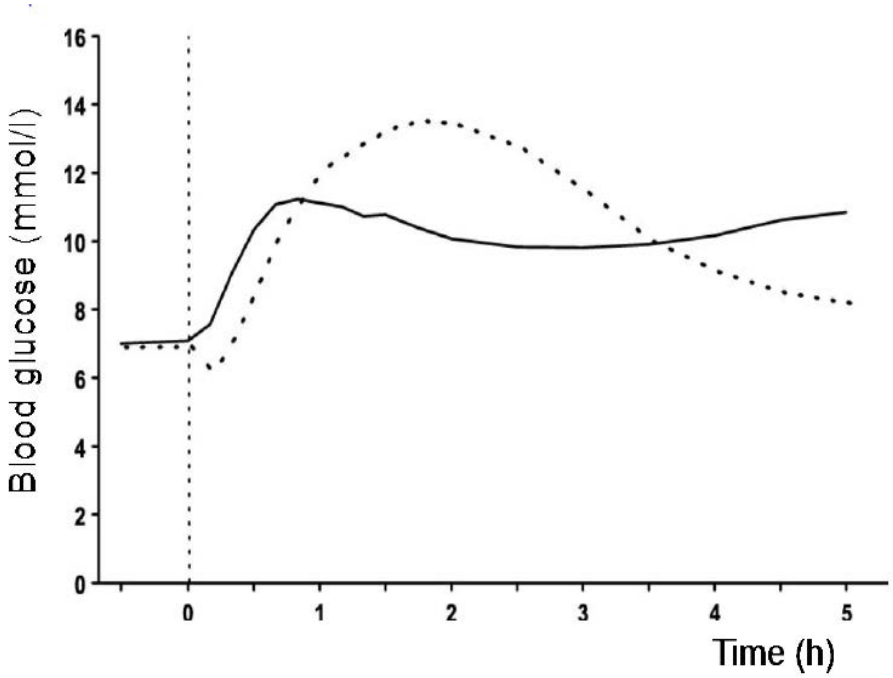

Fig. 1. Blood glucose concentrations following a single pre-meal dose of insulin aspart injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (hatched curve) in patients with type 1 diabetes mellitus.

When insulin aspart is injected subcutaneously, the onset of action will occur within 10 to 20 minutes of injection. The maximum effect is exerted between 1 and 3 hours after injection. The duration of action is 3 to 5 hours.

Clinical efficacy and safety

Clinical trials in patients with type 1 diabetes have demonstrated a lower postprandial blood glucose with insulin aspart compared to soluble human insulin (Fig. I). In two long-term open label trials in patients with type 1 diabetes comprising 1070 and 884 patients, respectively, insulin aspart reduced glycated haemoglobin by 0.12 [95% C.I. 0.03; 0.22] percentage points and by 0.15 [95% C.I. 0.05; 0.26] percentage points compared to human insulin; a difference of limited clinical significance.

Clinical trials in patients with type 1 diabetes have demonstrated a reduced risk of nocturnal hypoglycaemia with insulin aspart compared with soluble human insulin. The risk of daytime hypoglycaemia was not significantly increased.

Insulin aspart is equipotent to soluble human insulin on a molar basis.

Special populations

Elderly (≥ 65 years old)

A randomised, double-blind cross-over PK/PD trial comparing insulin aspart with soluble human insulin was performed in elderly patients with type 2 diabetes (19 patients aged 65-83 years, mean age 70 years). The relative differences in the pharmacodynamic properties (GIR_{max}, $AUC_{GIR,\ 0\text{-}120\ min}$) between insulin aspart and soluble human insulin in the elderly were similar to those seen in healthy subjects and in younger patients with diabetes.

Paediatric population
A clinical trial comparing preprandial soluble human insulin with postprandial insulin aspart was performed in small children (20 patients aged 2 to less than 6 years, studied for 12 weeks, among those four were younger than 4 years old) and a single dose PK/PD trial was performed in children (6-12 years) and adolescents (13-17 years). The pharmacodynamic profile of insulin aspart in children was similar to that seen in adults.

The efficacy and safety of insulin aspart given as bolus insulin in combination with either insulin detemir or insulin degludec as basal insulin has been studied for up to 12 months, in two randomised controlled clinical trials in adolescents and children aged 1 to less than 18 years (n=712). The trials included 167 children aged 1-5 years, 260 aged 6-11 and 285 aged 12-17. The observed improvements in HbA1c and the safety profiles were comparable between all age groups.

Pregnancy
A clinical trial comparing safety and efficacy of insulin aspart vs. human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies (insulin aspart: 157; human insulin: 165)) did not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn.

In addition the data from a clinical trial including 27 women with gestational diabetes randomised to treatment with insulin aspart vs. human insulin (insulin aspart: 14; human insulin: 13) showed similar safety profiles between treatments.

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

In Kixelle substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin. Kixelle is therefore more rapidly absorbed from the subcutaneous layer compared to soluble human insulin.

The time to maximum concentration is, on average, half of that for soluble human insulin. A mean maximum plasma concentration of 492±256 pmol/l was reached 40 (interquartile range: 30-40) minutes after a subcutaneous dose of 0.15 unit/kg bodyweight in type 1 diabetic patients. The insulin concentrations returned to baseline about 4 to 6 hours after dose. The absorption rate was somewhat slower in type 2 diabetic patients, resulting in a lower C_{max} (352±240 pmol/l) and later t_{max} (60 (interquartile range: 50-90) minutes). The intra-individual variability in time to maximum concentration is significantly less for Kixelle than for soluble human insulin, whereas the intra-individual variability in C_{max} for Kixelle is larger.

Special populations

Elderly (≥ 65 years old)
The relative differences in pharmacokinetic properties between insulin aspart and soluble human insulin in elderly patients (65-83 years, mean age 70 years) with type 2 diabetes were similar to those observed in healthy subjects and in younger patients with diabetes. A decreased absorption rate was observed in elderly patients, resulting in a later t_{max} (82 (interquartile range: 60-120) minutes), whereas C_{max} was similar to that observed in younger patients with type 2 diabetes and slightly lower than in patients with type 1 diabetes.

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 patients with hepatic impairment, absorption rate was decreased and more variable, resulting in delayed t_{max} from about 50 min in subjects with normal hepatic function to about 85 min in patients with moderate and severe hepatic impairment. AUC, C_{max} and CL/F were similar in patients with reduced hepatic function compared with subjects with normal hepatic function.

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

Paediatric population
The pharmacokinetic and pharmacodynamic properties of insulin aspart were investigated in children (6-12 years) and adolescents (13-17 years) with type 1 diabetes. Insulin aspart was rapidly absorbed in both age groups, with similar t_{max} as in adults. However, C_{max} differed between the age groups, stressing the importance of the individual titration of insulin aspart.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

In *in vitro* tests, including binding to insulin and IGF-1 receptor sites and effects on cell growth, insulin aspart behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of insulin aspart is equivalent to human insulin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Phenol
Metacresol
Zinc chloride
Disodium phosphate dihydrate
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be diluted or mixed with other medicinal products.

6.3 Shelf life

Before opening

30 months

After first opening

28 days

Chemical and physical in-use stability has been demonstrated for 31 days at 30°C and 5°C. From a microbiological point of view, once opened, the medicinal product may be stored for a maximum of 28 days at 30°C. Other in-use storage times are the responsibility of the user.

Kixelle 100 units/ml solution for injection in vial
Store below 30°C. Do not refrigerate. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Kixelle 100 units/ml solution for injection in pre-filled pen
Store below 30°C. Can be stored in a refrigerator (2°C-8°C). Do not freeze.
Keep the pen cap on the pen in order to protect from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.
Keep the medicinal product in the outer carton in order to protect from light.

For storage conditions of the medicinal product after first opening, see section 6.3.

6.5 Nature and contents of container

Kixelle 100 units/ml solution for injection in vial

10 ml solution in vial (type 1 glass) closed with a bromobutyl rubber stopper and aluminium flip-off seal.

Pack sizes of 1, or 5 vials or a multipack containing 5 (5 packs of 1) vials.

Kixelle 100 units/ml solution for injection in pre-filled pen

3 ml solution in cartridge (type 1 glass) with a plunger and stopper (bromobutyl) and aluminium seal contained in a multidose pre-filled pen.

Pack sizes of 1, 5, 10 pre-filled pens, or a multipack containing 10 (2 packs of 5) pre-filled pens.

6.6 Special precautions for disposal and other handling

Do not use this medicinal product if you notice that the solution is not clear, colourless and aqueous.

Kixelle which has been frozen must not be used.

The patient should be advised to discard the needle after each injection.

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

Needles, syringes, and pre-filled pens must not be shared.

Kixelle 100 units/ml solution for injection in vial

Kixelle may be used in an infusion pump system (CSII) as described in section 4.2. Tubings in which the inner surface materials are made of polyethylene or polyolefin have been evaluated and found compatible with pump use.

Kixelle 100 units/ml solution for injection in pre-filled pen

The needle sizes compatible with this pen are:
- 31G, 5 mm,
- 32G, 4-6 mm,
- 34G, 4 mm.

7. MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade, Baldoyle Industrial Estate, Dublin 13, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1506/001
EU/1/20/1506/002
EU/1/20/1506/003
EU/1/20/1506/004
EU/1/20/1506/005
EU/1/20/1506/006
EU/1/20/1506/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Biocon Sdn. Bhd.,
No. 1, Jalan Bioteknologi 1,
Kawasan Perindusterian SiLC
79200 Iskandar Puteri,
Johor,
Malaysia

Name and address of the manufacturer responsible for batch release

Kixelle vial and pre-filled pen:
McDermott Laboratories T/A Mylan Dublin Biologics Newenham Court Northern Cross Malahide Road Dublin, 17, Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (VIAL)

1. NAME OF THE MEDICINAL PRODUCT

Kixelle 100 units/ml solution for injection
insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 10 ml equivalent to 1,000 units. 1 ml solution contains 100 units insulin aspart (equivalent to 3.5 mg).

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc chloride, disodium hydrogen phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous or intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use solution only if clear and colourless.

8. EXPIRY DATE

EXP
After first use: Use within 28 days

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator.
After first use: Store below 30°C. Do not refrigerate. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade, Baldoyle Industrial Estate, Dublin 13,
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1506/001 1 vial of 10 ml
EU/1/20/1506/002 5 vials of 10 ml

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kixelle

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACK (VIAL - with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Kixelle 100 units/ml solution for injection
insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 10 ml equivalent to 1,000 units. 1 ml solution contains 100 units insulin aspart (equivalent to 3.5 mg).

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc chloride, disodium hydrogen phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 5 (5 packs of 1 x 10 ml) vials

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous or intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use solution only if clear and colourless.

8. EXPIRY DATE

EXP
After first use: Use within 28 days

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator.
After first use: Store below 30°C. Do not refrigerate. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade, Baldoyle Industrial Estate, Dublin 13,
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1506/003 5 packs of 1 x 10 ml vial

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kixelle

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON FOR MULTIPACK (VIAL - without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Kixelle 100 units/ml solution for injection
insulin aspart

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 10 ml equivalent to 1,000 units. 1 ml solution contains 100 units insulin aspart (equivalent to 3.5 mg).

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc chloride, disodium hydrogen phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial of 10 ml. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous or intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use solution only if clear and colourless

8. EXPIRY DATE

EXP/
After first use: Use within 28 days

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator.
After first use: Store below 30°C. Do not refrigerate. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade, Baldoyle Industrial Estate, Dublin 13,
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1506/003 5 packs of 1 x 10 ml vial

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kixelle

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING units

LABEL (VIAL)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

Kixelle 100 units/ml solution for injection
insulin aspart
SC, IV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (PRE-FILLED PEN.)

1. NAME OF THE MEDICINAL PRODUCT

Kixelle 100 units/ml solution for injection in pre-filled pen
insulin aspart

2 STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled pen contains 3 ml equivalent to 300 units. 1 ml solution contains 100 units insulin aspart (equivalent to 3.5 mg).

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 3 ml pre-filled pen
5 x 3 ml pre-filled pens
10 x 3 ml pre-filled pens

5. METHOD AND ROUTES OF ADMINISTRATION

Needles are not included.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use solution only if clear and colourless.
For use by one person only.
Only use needles that are compatible for use with this pre-filled pen.

8. EXPIRY DATE

EXP
After first use: Use within 28 days

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator.
After first use: Store below 30°C. Can be stored in a refrigerator. Do not freeze.
Keep the pen cap on in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade, Baldoyle Industrial Estate, Dublin 13,
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1506/004 1 pen of 3ml
EU/1/20/1506/005 5 pens of 3ml
EU/1/20/1506/006 10 pens of 3ml

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kixelle pre-filled pen

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER WRAPPER LABEL ON MULTIPACK (PRE-FILLED PEN - with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Kixelle 100 units/ml solution for injection in pre-filled pen
insulin aspart

2 STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled pen contains 3 ml equivalent to 300 units. 1 ml solution contains 100 units insulin aspart (equivalent to 3.5 mg).

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 10 (2 packs of 5) pre-filled pens

5. METHOD AND ROUTES OF ADMINISTRATION

Needles are not included.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use solution only if clear and colourless.
For use by one person only.
Only use needles that are compatible for use with this pre-filled pen.

8. EXPIRY DATE

EXP
After first use: Use within 28 days

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator.
After first use: Store below 30°C. Can be stored in a refrigerator. Do not freeze.
Keep the pen cap on in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade, Baldoyle Industrial Estate, Dublin 13,
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1506/007 10 (2 x 5) pens of 3ml

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kixelle pre-filled pen

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
INNER CARTON FOR MULTIPACK (PRE-FILLED PEN - without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Kixelle 100 units/ml solution for injection in pre-filled pen
insulin aspart

2 STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled pen contains 3 ml equivalent to 300 units. 1 ml solution contains 100 units insulin aspart (equivalent to 3.5 mg).

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide for pH adjustment and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

5 x 3 ml pre-filled pens. Component of a multipack cannot be sold separately.

5. METHOD AND ROUTES OF ADMINISTRATION

Needles are not included.
Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Use solution only if clear and colourless.
For use by one person only.
Only use needles that are compatible for use with this pre-filled pen.

8. EXPIRY DATE

EXP/
After first use: Use within 28 days

9. SPECIAL STORAGE CONDITIONS

Before opening: Store in a refrigerator.
After first use: Store below 30°C. Can be stored in a refrigerator. Do not freeze.
Keep the pen cap on in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade, Baldoyle Industrial Estate, Dublin 13,
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1506/007 2 x 5 pens of 3ml

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kixelle pre-filled pen

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING units

PEN LABEL (PRE-FILLED PEN)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

Kixelle 100 units/ml solution for injection
insulin aspart
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Kixelle 100 units/ ml solution for injection in vial
insulin aspart

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kixelle is and what it is used for
2. What you need to know before you use Kixelle
3. How to use Kixelle
4. Possible side effects
5. How to store Kixelle
6. Contents of the pack and other information

1. What Kixelle is and what it is used for

Kixelle is a modern insulin (insulin analogue) with a rapid-acting effect. Modern insulin products are improved versions of human insulin.

Kixelle is used to reduce the high blood sugar level in adults, adolescents and children aged 1 year and above with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. Treatment with Kixelle helps to prevent complications from your diabetes.

Kixelle will start to lower your blood sugar 10-20 minutes after you inject it, a maximum effect occurs between 1 and 3 hours after the injection and the effect lasts for 3-5 hours. Due to this short action Kixelle should normally be used in combination with intermediate-acting or long-acting insulin preparations. Moreover Kixelle can be used for continuous infusion in a pump system.

2. What you need to know before you use Kixelle

Do not use Kixelle
- If you are allergic to insulin aspart, or any of the other ingredients of this medicine (listed in section 6).
- If you suspect hypoglycaemia (low blood sugar) is starting (see a) Summary of serious and very common side effects in section 4).
- If the protective cap is loose or missing. Each vial has a protective, tamper-proof plastic cap. If it is not in perfect condition when you get the vial, return the vial to your supplier.
- If it has not been stored correctly or been frozen (see section 5, How to store Kixelle).
- If the insulin does not appear clear and colourless.

If any of these applies, do not use Kixelle. Talk with your doctor, nurse or pharmacist for advice.

Before using Kixelle
- Check the label to make sure it is the right type of insulin.
- Remove the protective cap.
- Always use a new needle for each injection to prevent contamination.
- Needles and syringes must not be shared.

Warnings and precautions
- Some conditions and activities can affect your need for insulin. Consult your doctor:
- If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.
- If you are ill, carry on using your insulin and consult your doctor.
- If you are going abroad, travelling over time zones may affect your insulin needs and the timing of your injections.

Skin changes at the injection site
The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area (see section 3, How to use Kixelle). Tell your doctor if you notice any skin changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Children and adolescents
Do not give this medicine to children below 1 year of age since no clinical studies have been carried out in children below the age of 1 year.

Other medicines and Kixelle
Tell your doctor, nurse or pharmacist if you are taking, have recently used or might use any other medicines.
Some medicines affect your blood sugar level and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you use:
- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulphonamides (used to treat infections).

Your blood sugar level may rise (hyperglycaemia) if you use:
- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as ‘cortisone’ used to treat inflammation)
- Thyroid hormones (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body’s metabolic processes)
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Pioglitazone (tablets used for the treatment of type 2 diabetes)
Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have used any of the medicines listed here, tell your doctor, nurse or pharmacist.

Kixelle and alcohol
- If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Kixelle can be used during pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.
- There are no restrictions on treatment with Kixelle during breast-feeding.

Ask your doctor, nurse or pharmacist for advice before using this medicine while pregnant or breast-feeding.

Driving and using machines
Please ask your doctor whether you can drive a car or operate a machine:
- If you have frequent hypoglycaemia.
- If you find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, your concentration and ability to react might be affected and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Kixelle has a rapid onset of effect therefore if hypoglycaemia occurs, you may experience it earlier after an injection when compared to soluble human insulin.

Kixelle contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use Kixelle

Dose and when to use your insulin
Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

Kixelle is generally used immediately before a meal. Eat a meal or snack within 10 minutes of the injection to avoid low blood sugar. When necessary, Kixelle can be given soon after a meal. See How and where to inject below for information.

Do not change your insulin unless your doctor tells you to. If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Use in children and adolescents
Kixelle can be used in adolescents and children aged 1 year and above instead of soluble human insulin when a rapid onset of effect is preferred. For example, when it is difficult to dose the child in relation to meals.

Use in special patient groups
If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How and where to inject
Kixelle is for injection under the skin (subcutaneously). or for continuous infusion in a pump system. Administration in a pump system will require a comprehensive instruction by your healthcare professional. You must never inject yourself directly into a vein (intravenously) or muscle (intramuscularly). If necessary Kixelle can be given directly into a vein but this must only be done by physicians or other healthcare staff.

With each injection, change the injection site within the particular area of skin that you use. This may reduce the risk of developing lumps or skin pitting (see section 4, Possible side effects). The best places to give yourself an injection are the front of your waist (abdomen), the upper arm or the front of your thighs. The insulin will work more quickly if injected into the front of your waist. You should always measure your blood sugar regularly.

How to use Kixelle
1. Draw into the syringe the same amount of air as the dose of insulin you are going to inject. Inject the air into the vial.
2. Turn the vial and syringe upside down and draw the correct insulin dose into the syringe. Pull the needle out of the vial. Then expel the air from the syringe and check that the dose is correct.

How to inject Kixelle
- Inject the insulin under the skin. Use the injection technique advised by your doctor or nurse.
- Keep the needle under your skin for at least 6 seconds to make sure you have injected all the insulin.
- Discard the needle after each injection.

For use in an infusion pump system
Kixelle should never be mixed with any other insulin when used in a pump.
Follow the instructions and recommendations from your doctor regarding the use of Kixelle in a pump. Before use of Kixelle in the pump system, you must have received a comprehensive instruction in the use and information about any actions to be taken in case of illness, too high or too low blood sugar or failure of the pump system.
- Before inserting the needle, use soap and water to clean your hands and the skin where the needle is inserted to avoid any infection at the infusion site.
- When you fill a new reservoir, be certain not to leave large air bubbles in either the syringe or the tubing.
- Changing of the infusion set (tubing and needle) must be done according to the instructions in the product information supplied with the infusion set.

To get the benefit of insulin infusion, and to detect possible malfunction of the insulin pump, it is recommended that you measure your blood sugar level regularly.

What to do in case of pump system failure
You should always have an alternative delivery method for your insulin available for injection under the skin in case of pump system failure.

If you use more insulin than you should
If you use too much insulin your blood sugar gets too low (hypoglycaemia). See a) Summary of serious and very common side effects in section 4.

If you forget to use your insulin
If you forget to use your insulin your blood sugar may get too high (hyperglycaemia). See c) Effects from diabetes in section 4.

If you stop using your insulin
Do not stop using your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See c) Effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

a) Summary of serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect. It may affect more than 1 in 10 people.

Low blood sugar may occur if you:
- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (see Drinking alcohol and taking Kixelle in section 2).

Signs of low blood sugar:
Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. You may recover more quickly from unconsciousness with an injection of the hormone glucagon by someone who knows how to use it. If you are given glucagon, you will need glucose or a sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:
- If you experience low blood sugar, eat glucose tablets or another high sugar snack (e.g. sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets or high sugar snacks with you, just in case.
- When symptoms of low blood sugar have disappeared or when blood sugar level is stabilised, continue insulin treatment as usual.
- If you have such a low blood sugar that it makes you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (become unconscious) due to low blood sugar. Let them know that if you pass out, they

must turn you on your side and get medical help straight away. They must not give you any food or drink due to risk of suffocation.

Serious allergic reactions to Kixelle or one of its ingredients (called a systemic allergic reaction) is a very rare side effect but can potentially be life threatening. It may affect up to 1 in 10,000 people.

Seek medical advice immediately:
- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.

If you notice any of these signs, seek medical advice immediately.

Skin changes at the injection site: If you inject insulin at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect up to 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

b) List of other side effects

Uncommon side effects (may affect up to 1 in 100 people)

Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur. These usually disappear after a few weeks of using your insulin. If they do not disappear, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.

Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Swollen joints: When you start using insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears. If not, talk to your doctor.

Diabetic retinopathy: (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects (may affect up to 1 in 1,000 people)

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to inject your insulin or stop using insulin.
- Repeatedly inject less insulin than you need.

- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar: The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed; dry skin; dry mouth and a fruity (acetone) smell of the breath.

What to do if you experience high blood sugar:
- If you get any of the above signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
- These may be signs of a very serious condition called diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

5. How to store Kixelle

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after 'EXP'. The expiry date refers to the last day of that month.

Keep the medicine in the outer carton in order to protect from light.

Before opening: Store in a refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

After first opening: The medicine may be stored for a maximum of 28 days. Store below 30°C. Do not refrigerate or freeze.

Discard the needle after each injection.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Kixelle contains
- The active substance is insulin aspart. Each ml contains 100 units of insulin aspart. Each vial contains 1,000 units of insulin aspart in 10 ml solution for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide (see section 2 "Kixelle contains sodium"), and water for injections.

What Kixelle looks like and contents of the pack
Kixelle is presented as a solution for injection (injection). The solution is clear and colourless.

Pack sizes of 1, or 5 vials or a multipack containing 5 packs of 1 vial.
Not all pack sizes may be marketed.

The solution is clear and colourless.

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Manufacturer
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the user

Kixelle 100 units/ml solution for injection in pre-filled pen
insulin aspart

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kixelle is and what it is used for
2. What you need to know before you use Kixelle
3. How to use Kixelle
4. Possible side effects
5. How to store Kixelle
6. Contents of the pack and other information

1. What Kixelle is and what it is used for

Kixelle is a modern insulin (insulin analogue) with a rapid-acting effect. Modern insulin products are improved versions of human insulin.

Kixelle is used to reduce the high blood sugar level in adults, adolescents and children aged 1 year and above with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. Treatment with Kixelle helps to prevent complications from your diabetes.

Kixelle will start to lower your blood sugar 10-20 minutes after you inject it, a maximum effect occurs between 1 and 3 hours after the injection and the effect lasts for 3-5 hours. Due to this short action Kixelle should normally be used in combination with intermediate-acting or long-acting insulin preparations.

2. What you need to know before you use Kixelle

Do not use Kixelle
- If you are allergic to insulin aspart, or any of the other ingredients of this medicine listed in section 6.
- If you suspect hypoglycaemia (low blood sugar) is starting (see a) Summary of serious and very common side effects in section 4).
- If Kixelle is dropped, damaged or crushed.
- If it has not been stored correctly or been frozen (see section 5, How to store Kixelle).
- If the insulin does not appear clear and colourless.

If any of these applies, do not use Kixelle. Talk with your doctor, nurse or pharmacist for advice.

Before using Kixelle
- Check the label to make sure it is the right type of insulin.
- Always use a new needle for each injection to prevent contamination.
- Needles and Kixelle pre-filled pen must not be shared.
- Kixelle pre-filled pen is only suitable for injecting under the skin. Speak to your doctor if you need to inject your insulin by another method.

Warnings and precautions
- Some conditions and activities can affect your need for insulin. Consult your doctor:
- If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- If you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.
- If you are ill, carry on using your insulin and consult your doctor.
- If you are going abroad, travelling over time zones may affect your insulin needs and the timing of your injections.

Skin changes at the injection site
The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area (see section 3, How to use Kixelle). Tell your doctor if you notice any skin changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Children and adolescents
Do not give this medicine to children below 1 year of age since no clinical studies have been carried out in children below the age of 1 year.

Other medicines and Kixelle
Tell your doctor, nurse or pharmacist if you are taking, have recently used or might use any other medicines.
Some medicines affect your blood sugar level and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you use:
- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulphonamides (used to treat infections).

Your blood sugar level may rise (hyperglycaemia) if you use:
- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as ‘cortisone’ used to treat inflammation)
- Thyroid hormones (used to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body’s metabolic processes)

- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Pioglitazone (tablets used for the treatment of type 2 diabetes)
Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have used any of the medicines listed here, tell your doctor, nurse or pharmacist.

Kixelle and alcohol
- If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Kixelle can be used during pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.
- There are no restrictions on treatment with Kixelle during breast-feeding.

Ask your doctor, nurse or pharmacist for advice before using this medicine while pregnant or breast-feeding.

Driving and using machines
Please ask your doctor whether you can drive a car or operate a machine:
- If you have frequent hypoglycaemia.
- If you find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, your concentration and ability to react might be affected and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Kixelle has a rapid onset of effect therefore if hypoglycaemia occurs, you may experience it earlier after an injection when compared to soluble human insulin.

Kixelle contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

3. How to use Kixelle

Dose and when to use your insulin
Always use your insulin and adjust your dose exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Kixelle is generally used immediately before a meal. Eat a meal or snack within 10 minutes of the injection to avoid low blood sugar. When necessary, Kixelle can be given soon after a meal. See How and where to inject below for information.

Do not change your insulin unless your doctor tells you to. If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Use in children and adolescents
Kixelle can be used in adolescents and children aged 1 year and above instead of soluble human insulin when a rapid onset of effect is preferred. For example, when it is difficult to dose the child in relation to meals.

Use in special patient groups
If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How and where to inject
Kixelle is for injection under the skin (subcutaneously). You must never inject yourself directly into a vein (intravenously) or muscle (intramuscularly). Kixelle pre-filled pen is only suitable for injecting under the skin. Speak to your doctor if you need to inject your insulin by another method.

With each injection, change the injection site within the particular area of skin that you use. This may reduce the risk of developing lumps or skin pitting (see section 4, Possible side effects). The best places to give yourself an injection are the front of your waist (abdomen), the upper arm or the front of your thighs. The insulin will work more quickly if injected into the front of your waist. You should always measure your blood sugar regularly.

How to handle Kixelle pre-filled pen
Kixelle pre-filled pen is a pre-filled, disposable pen containing insulin aspart.

Read carefully the instructions on how to use Kixelle pre-filled pen included in this package leaflet. You must use the pen as described in the instructions on how to use Kixelle pre-filled pen.

Always ensure you use the correct pen before you inject your insulin.

If you use more insulin than you should
If you use too much insulin your blood sugar gets too low (hypoglycaemia). See a) Summary of serious and very common side effects in section 4.

If you forget to use your insulin
If you forget to use your insulin your blood sugar may get too high (hyperglycaemia). See c) Effects from diabetes in section 4.

If you stop using your insulin
Do not stop using your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See c) Effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

a) Summary of serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect. It may affect more than 1 in 10 people.

Low blood sugar may occur if you:
- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (see Drinking alcohol and using Kixelle in section 2).

Signs of low blood sugar: Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. You may recover more quickly from unconsciousness with an injection of the hormone glucagon by someone who knows how to use it. If you are given glucagon, you will need glucose or a sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:
- If you experience low blood sugar, eat glucose tablets or another high sugar snack (e.g. sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets or high sugar snacks with you, just in case.
- When symptoms of low blood sugar have disappeared or when blood sugar level is stabilised, continue insulin treatment as usual.
- If you have such a low blood sugar that it makes you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (become unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink due to risk of suffocation.

Serious allergic reactions to Kixelle or one of its ingredients (called a systemic allergic reaction) is a very rare side effect but can potentially be life threatening. It may affect up to 1 in 10,000 people.

Seek medical advice immediately:
- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.

If you notice any of these signs, seek medical advice immediately.

Skin changes at the injection site: If you inject insulin at the same place, the fatty tissue may shrink (lipoatrophy) or thicken (lipohypertrophy) (may affect up to 1 in 100 people). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis; how often this occurs is not known). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

b) List of other side effects

Uncommon side effects (may affect up to 1 in 100 people)

Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur. These usually disappear after a few weeks of using your insulin. If they do not disappear, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.

Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Swollen joints: When you start using insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears. If not, talk to your doctor.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects (may affect up to 1 in 1,000 people)

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

c) Effects from diabetes

High blood sugar (hyperglycaemia)

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to inject your insulin or stop using insulin.
- Repeatedly inject less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar: The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed; dry skin; dry mouth and a fruity (acetone) smell of the breath.

What to do if you experience high blood sugar:
- If you get any of the above signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
- These may be signs of a very serious condition called diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

5. How to store Kixelle

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled pen label and carton after 'EXP'. The expiry date refers to the last day of that month.

Keep the medicine in the outer carton in order to protect from light.

Before opening: Kixelle pre-filled pen that is not being used is to be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

After first use: You can carry your Kixelle pre-filled pen with you and keep it at a temperature below 30°C or in a refrigerator (2 ˚C to 8 ˚C) for up to 28 days. If refrigerated, keep away from the cooling element. Do not freeze.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Kixelle pre-filled pen contains
- The active substance is insulin aspart. Each ml contains 100 units of insulin aspart. Each pre-filled pen contains 300 units in insulin aspart in 3 ml solution for injection.
- The other ingredients are glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide (see section 2 "Kixelle contains sodium"), and water for injections.

What Kixelle looks like and contents of the pack
Pre-filled plastic pen with cap containing 3 ml of clear colourless solution.

Pack sizes of 1, 5, 10 pre-filled pens, or a multipack containing 10 (2 packs of 5) pre-filled pens.
Not all pack sizes may be marketed.

The solution is clear and colourless.

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {**MM/YYYY**}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Kixelle pre-filled pen
INSTRUCTIONS FOR USE

Read the following instructions, as well as the package leaflet carefully before using your Kixelle pre-filled pen.

If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

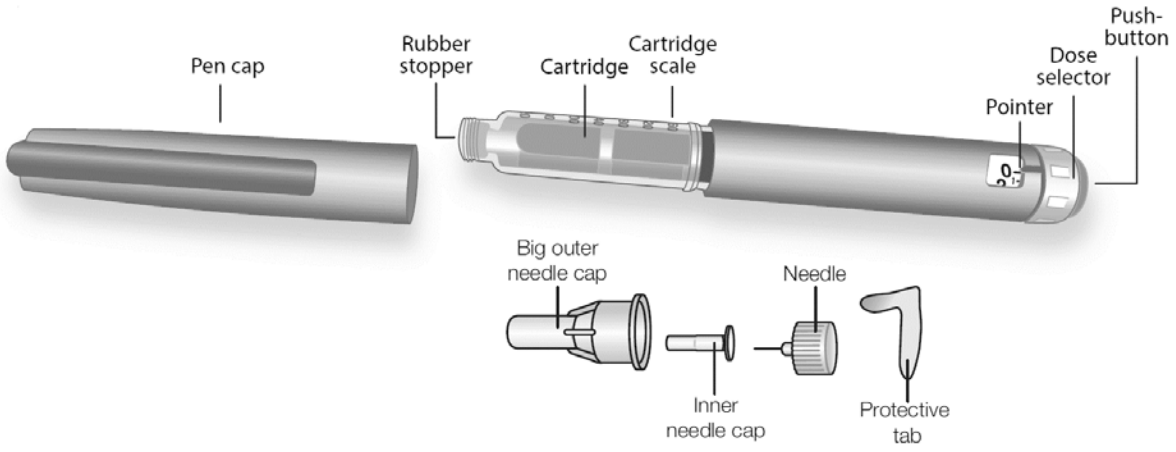
Kixelle pre-Filled pen is a prefilled dial-a-dose insulin pen. You can select doses from 1 to 80 units in increments of 1 unit.

Needle sizes compatible with this pen:

- 31G, 5 mm
- 32G, 4 mm
- 34G, 4 mm

As a precautionary measure, always carry a spare insulin delivery device in case your Kixelle pre-filled pen is lost or damaged.

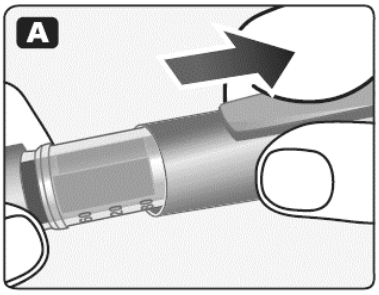
Kixelle pre-filled pen



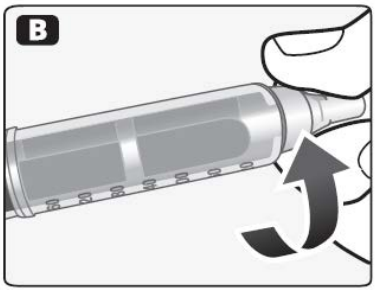
Each time you use the pen

- Wash your hands before using the pen
- Check the name and coloured label of your pen to make sure that it contains the correct type of insulin. This is especially important if you use more than one type of insulin. If you use the wrong type of insulin, your blood sugar level may get too high or too low.
- Check the insulin in the cartridge. Kixelle should be clear, colourless and free of particles. If not, do not use.

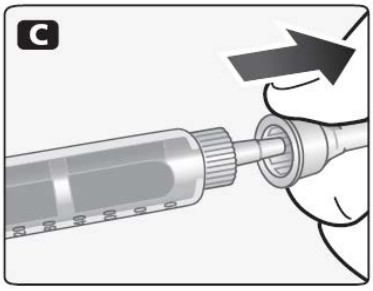
Step 1. Prepare your pen
1a- Pull of the pen cap (see figure A)
1b- Wipe the rubber stopper with an alcohol swab



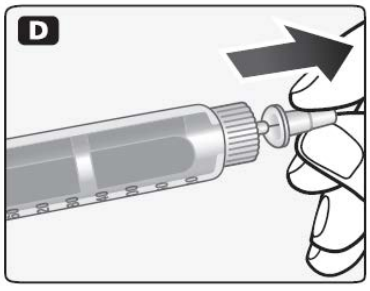
Step 2. Attach the needle
2a- Remove the paper tab from a new disposable needle.
2b- Screw the needle straight and tightly onto your Kixelle pre-filled pen (see figure B).



2c- Pull off the big outer needle cap and keep it for later (see figure C)



2d- Pull off the inner needle cap and dispose of it (see figure D).
Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.



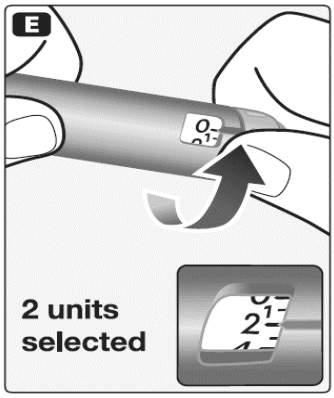
Important information:

- Always use a new needle for each injection. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

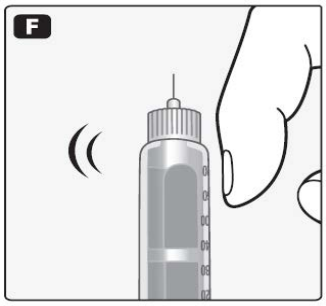
- Be careful not to bend or damage the needle before use.

Step 3. Checking the insulin flow
Prior to each injection small amounts of air may collect in the cartridge during normal use. To avoid injection of air and ensure proper dosing

3a- Turn the dose selector to select 2 units (see figure E)



3b- Hold your Kixelle Pre-Filled Pen with the needle pointing upwards and tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge (see figure F)



3c- Keeping the needle upwards, press the push-button all the way in. The dose selector returns to 0. A drop of insulin should appear at the needle tip (see figure G). If not, change the needle and repeat procedure from step 3a to 3c no more than 6 times. If a drop of insulin still does not appear, the pen is defective, and you must use a new one.

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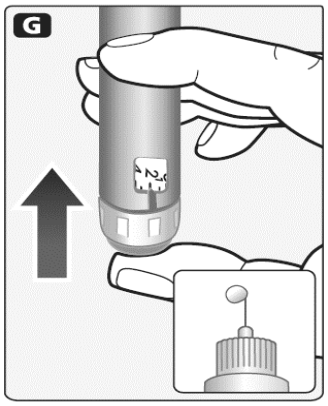


Important information:

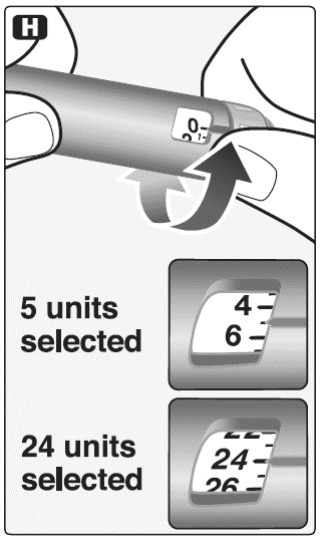
- Always make sure that a drop appears at the needle tip before you inject. This makes sure that the insulin flows. If no drop appears, you will not inject any insulin, even though the dose selector may move. This may indicate a blocked or damaged needle.

- Always check the flow before you inject. If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

Step 4: Selecting your dose

4a- Check that the dose selector is set at 0.

4b- Turn the dose selector to the number of units you need to inject (see figure H).
The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer. When turning the dose selector, be careful not to push the push button as insulin will come out. You cannot select a dose larger than the number of units left in the cartridge



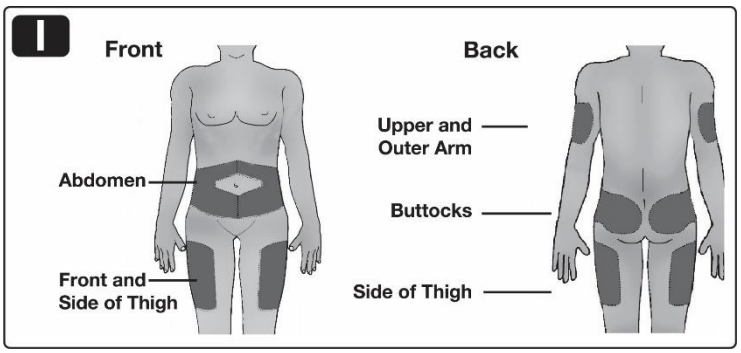
Important information:

- Always use the dose selector and the pointer to see how many units you have selected before injecting the insulin.

- Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low. Do not use the residual scale, it only shows approximately how much insulin is left in your pen.

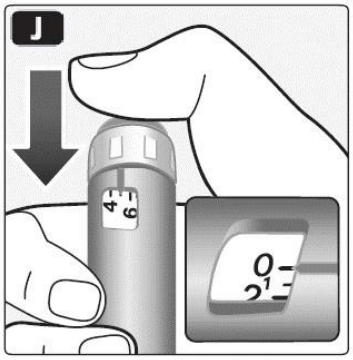
Step 5. Giving the injection

5a- Use the injection technique shown by your doctor or nurse.
Kixelle pre-filled pen can be injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs (thighs) or upper arms (see figure I).

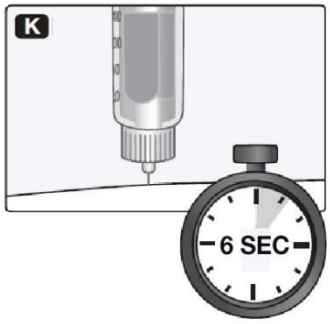


5b- For each injection change (rotate) your injection site within the area of skin that you use. **Do not** use the same injection site for each injection.

5c- Insert the needle into your skin. Inject the dose by pressing the push button all the way in until 0 lines up with the pointer (see figure J). Be careful only to push the push button when injecting.



5d- Keep the push-button fully depressed and let the needle remain under the skin for at least 6 seconds (see figure K). This will make sure you get the full dose.



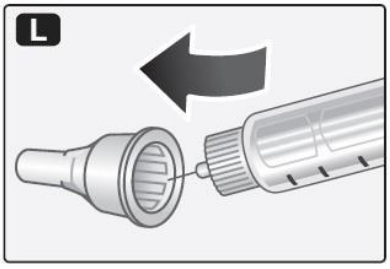
5e- After holding and slowly counting to 6, withdraw the needle from the skin, then release the pressure on the push-button.

Important information:

- Always make sure that the dose selector returns to 0 after the injection. If the dose selector stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.

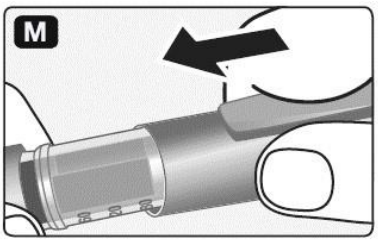
Step 6: After the injection

6a- Carefully put the outer needle cap over the needle (see figure L).
Unscrew the needle. Safely remove the needle from your Kixelle pre-filled pen after each use.



Dispose of needle in a suitable sharps container.

6b. Put the pen cap on the Kixelle pre-filled pen (see figure M) and store the pen without the needle attached.



Caring for your pen

Your Kixelle Pre-Filled Pen must be handled with care. If it is dropped, damaged, or crushed, there is a risk of insulin leakage. This may cause inaccurate dosing, which can lead to too high or too low blood sugar level.

You can clean the exterior of your Kixelle Pre-Filled Pen by wiping it with a medicinal swab. Do not soak it, wash or lubricate it as it may damage the pen.

Do not refill your Kixelle Pre-Filled Pen. Once empty, it must be disposed of.

Further important information

• Caregivers must be very careful when handling used needles to reduce the risk of needle sticks and cross-infection.

• Dispose of your used Kixelle Pre-Filled Pen carefully without the needle attached.

• Never share your pen or your needles with other people. It might lead to cross-infection.

• Never share your pen with other people. Your medicine might be harmful to their health.

• Always keep your pen and needles out of sight and reach of others, especially children.