

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

Medicinal product no longer authorised

## 1. NAME OF THE MEDICINAL PRODUCT

Velosulin 100 IU/ml solution for injection or infusion in a vial.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insulin human, rDNA (produced by recombinant DNA technology in *Saccharomyces cerevisiae*).

1 ml contains 100 IU of insulin human.

1 vial contains 10 ml equivalent to 1000 IU.

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection or infusion in a vial.

Clear, colourless, aqueous solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of diabetes mellitus.

### 4.2 Posology and method of administration

This phosphate-buffered soluble insulin is intended for continuous subcutaneous insulin infusion (CSII) in external insulin infusion pumps.

Velosulin is a fast-acting insulin and may be used in combination with certain long-acting insulin products. For incompatibilities see section 6.2.

#### Dosage

Dosage is individual and determined by the physician in accordance with the needs of the patient.

Usually, 40-60% of the total daily dose is given as a continuous basal rate and the remaining 40-60% as boluses divided between the three main meals.

In general, when patients are transferred from injection to infusion therapy, it may be advisable to reduce the dosage by initiating the patient at 90% of the previous total daily dosage, with 40% as basal rate and 50% as boluses divided between the three main meals.

Dosage is individual and determined in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty or due to obesity) and lower in patients with residual, endogenous insulin production.

In patients with diabetes mellitus optimised glycaemic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.

An injection or infusion should be followed within 30 minutes by a meal or snack containing carbohydrates.

#### Dosage adjustment

Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement.

Renal or hepatic impairment may reduce insulin requirement.

Adjustment of dosage may also be necessary if patients change physical activity or their usual diet. Dosage adjustment may be necessary when transferring patients from one insulin preparation to another (see section 4.4 ).

#### Administration

For subcutaneous or intravenous use.

#### Insulin infusion (CSII):

Continuous subcutaneous insulin infusion (CSII) in external insulin infusion pumps is usually administered in the abdominal wall. Velosulin should never be mixed with any other insulin products when used in a pump.

Patients started on CSII must receive comprehensive instruction in the use of the pump, and the necessary actions in case of illness, hypoglycaemia, hyperglycaemia or pump failure.

The patient should read and follow the instructions that accompany the infusion pump and use the correct reservoir and catheter for the pump (see section 6.6).

The infusion set should be changed every 48 hours using aseptic technique when inserting the infusion set.

When filling a new syringe, no large air bubbles should be left in either the syringe or the catheter. The patient should follow the instructions from the physician about the basal infusion rate and the mealtime insulin boluses to be taken.

To get the benefit of insulin infusion, and to detect possible malfunction of the pump, the patient should measure his blood glucose level regularly.

In the event of a hypoglycaemic episode, the infusion should be stopped until the episode is resolved. If repeated or severe low blood glucose levels occur, the patient should notify the health care professional and the need to reduce or stop the insulin administration should be considered. A pump malfunction or obstruction of the infusion set can result in a rapid rise in glucose levels. If the patient suspects an interruption to insulin flow the patient should notify the health care professional.

Patients administering Velosulin by CSII must have injection syringes and alternative insulin readily available in case of emergency or pump interruption or failure, in order that insulin can be administered by subcutaneous injection.

#### Insulin injection:

Administration of Velosulin is also possible by subcutaneous or intravenous injection. Intravenous administration should only be carried out by health care professionals.

Velosulin is administered subcutaneously in the abdominal wall. The thigh, the gluteal region or the deltoid region may also be used.

Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.

Injection into a lifted skin fold minimises the risk of unintended intramuscular injection.

The needle should be kept under the skin for at least 6 seconds to make sure the entire dose is injected.

Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy.

The vials may be used with insulin syringes with a corresponding unit scale. When two types of insulin are mixed, draw the amount of fast-acting insulin first, followed by the amount of long-acting insulin.

Velosulin is accompanied by a package leaflet with detailed instruction for use to be followed.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).  
Hypoglycaemia.

### 4.4 Special warnings and precautions for use

Inadequate dosage or discontinuation of treatment, especially in type 1 diabetes, may lead to **hyperglycaemia**.

Usually, the first symptoms of hyperglycaemia set in 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.

Due to the lack of long-acting insulin, patients receiving continuous subcutaneous insulin infusion via an insulin pump are at risk of fast development of ketoacidosis in case of prolonged interruption of continuous subcutaneous insulin infusion.

**Hypoglycaemia** may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.8 and 4.9).

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

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, long-acting insulin etc.), origin (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dosage. If an adjustment is needed when switching the patients to Velosulin, it may occur with the first dose or during the first several weeks or months.

As with any insulin therapy, injection site reactions may occur and include pain, itching, hives, swelling and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of Velosulin.

A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.

Before travelling between different time zones, the patient should be advised to consult the physician, since this may mean that the patient has to take insulin and meals at different times.

Patients using CSII may be more prone to infection at the site of infusion. Infections can be minimised by careful attention to personal hygiene of the hands and infusion site and by frequent changes of catheter (maximum usage 2 days).

Velosulin contains metacresol, which may cause allergic reactions.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

A number of medicinal products are known to interact with glucose metabolism. The physician must therefore take possible interactions into account and should always ask his patients about any medicinal products they take.

##### **The following substances may reduce insulin requirement:**

Oral hypoglycaemic agents (OHA), monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, anabolic steroids or sulphonamides.

##### **The following substances may increase insulin requirement:**

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones and beta-sympathomimetics, growth hormone and danazol.

Beta-blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.

Octreotide/lanreotide may both decrease and increase insulin requirement.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

#### **4.6 Pregnancy and lactation**

There are no restrictions on treatment of diabetes with insulin during pregnancy, as insulin does not pass the placental barrier.

Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death *in utero*. Intensified control in the treatment of pregnant women with diabetes is therefore recommended throughout pregnancy and when contemplating pregnancy.

Insulin requirements usually fall in the first trimester and subsequently increase during the second and third trimesters.

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

Insulin treatment of the nursing mother presents no risk to the baby. However, the Velosulin dosage may need to be adjusted.

#### **4.7 Effects on ability to drive and use machines**

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

Patients should be advised to take precautions to avoid hypoglycaemia whilst 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

As for other insulin products, in general, hypoglycaemia is the most frequently occurring undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Frequencies of adverse drug reactions from clinical trials that are considered related to fast-acting human insulin (Actrapid) are listed below. The frequencies are defined as: uncommon ( $\geq 1/1,000$  to  $< 1/100$ ). Isolated spontaneous cases are presented as very rare defined as  $< 1/10,000$  including isolated reports.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

### Nervous system disorders

Uncommon - Peripheral neuropathy

Fast improvement in blood glucose control may be associated with a condition termed “acute painful neuropathy”, which is usually reversible.

### Eye disorders

Uncommon - Refraction disorders

Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

Very rare - Diabetic retinopathy

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

### Skin and subcutaneous tissue disorders

Uncommon – Lipodystrophy

Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

### General disorders and administration site conditions

Uncommon - Injection site reactions

Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are transitory and disappear during continued treatment.

Uncommon - Oedema

Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

### Immune system disorders

Uncommon - Urticaria, rash

Very rare - Anaphylactic reactions

Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness. Generalised hypersensitivity reactions are potentially life-threatening.

## 4.9 Overdose

A specific overdose of insulin cannot be defined. However, hypoglycaemia may develop over sequential stages:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patients carry some sugar lumps, sweets, biscuits or sugary fruit juice.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulins and analogues for injection, fast-acting, insulin (human). ATC code: A10A B01.

The blood glucose lowering effect of insulin 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.

A clinical trial in a single intensive care unit treating hyperglycaemia (blood glucose above 10 mmol/l) in 204 diabetic and 1344 non-diabetic patients undergoing major surgery showed that normoglycaemia (blood glucose 4.4 – 6.1 mmol/l) induced by intravenous treatment with another fast acting human insulin (Actrapid) reduced mortality by 42% (8% versus 4.6%).

Velosulin is a fast-acting insulin.

When Velosulin is administered as a bolus injection onset of action is within ½ hour, reaches a maximum effect within 1.5-3.5 hours and the entire duration of action is approximately 7-8 hours.

### 5.2 Pharmacokinetic properties

Insulin in the blood stream has a half-life of a few minutes. Consequently, the time-action profile of an insulin preparation is determined solely by its absorption characteristics.

This process is influenced by several factors (e.g. insulin dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin products are therefore affected by significant intra- and inter-individual variation.

Continuous subcutaneous infusion eliminates some of the variations/fluctuations inherent to injection therapy.

The relatively fast absorption of soluble insulin ensures a constant supply of insulin to the blood from a relatively small pool under the skin.

#### Absorption

The maximum plasma concentration is reached within 1.5-2.5 hours after subcutaneous administration.

### Distribution

No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.

### Metabolism

Human insulin is reported to be degraded by insulin protease or insulin-degrading enzymes and possibly protein disulfide isomerase. A number of cleavage (hydrolysis) sites on the human insulin molecule have been proposed; none of the metabolites formed following the cleavage are active.

### Elimination

The terminal half-life is determined by the rate of absorption from the subcutaneous tissue. The terminal half-life ( $t_{1/2}$ ) is therefore a measure of the absorption rather than of the elimination *per se* of insulin from plasma (insulin in the blood stream has a  $t_{1/2}$  of a few minutes). Trials have indicated a  $t_{1/2}$  of about 2-5 hours.

### Children and adolescents

The pharmacokinetic profile has been studied in a small number (n=18) of diabetic children (aged 6-12 years) and adolescents (aged 13-17 years) using another fast-acting human insulin, (Actrapid). The data are limited but suggest that the pharmacokinetic profile in children and adolescents may be similar to that in adults. However, there were differences between age groups in  $C_{max}$ , stressing the importance of individual dose titration.

## **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, carcinogenic potential, toxicity to reproduction.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

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

### **6.2 Incompatibilities**

Insulin products should only be added to compounds with which it is known to be compatible. Medicinal products added to the insulin solution may cause degradation of the insulin, e.g. if the medicinal products contain thiols or sulphites.

Concerning compatibility with insulin infusion pumps, reservoirs, catheters and needles, see section 6.6.

### **6.3 Shelf life**

30 months when stored between 2°C - 8°C.

6 weeks when used or stored at room temperature (below 25°C).



After first use as infusion, the insulin solution may be stored in the pump reservoir for six days at up to 37°C (close to the body).

#### **6.4 Special precautions for storage**

Before use: store in a refrigerator (2°C - 8°C).

Do not store them in or too near the freezer section or cooling element.

Do not freeze.

During use: do not refrigerate. Do not store above 25°C.

After first use as infusion: the insulin solution may be stored in the pump reservoir at up to 37°C (close to the body).

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

Protect from excessive heat and sunlight.

#### **6.5 Nature and contents of container**

10 ml glass vial (type 1) closed with a bromobutyl/polyisoprene rubber stopper and a protective tamper-proof cap.

Pack sizes: 1 and 5 vials x 10 ml and a multipack with 5 x (1 x 10 ml) vials.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal and other handling**

Upon mixing Velosulin with infusion fluids an unpredictable amount of insulin will be absorbed to the infusion material. Monitoring of the patient's blood glucose during infusion is therefore recommended.

When administered by CSII no other medicinal products or other insulin products should be mixed in the reservoir of the infusion pump with Velosulin.

When combination with long-acting insulin is necessary it is only possible to mix Velosulin with isophane or premixed insulin products. Velosulin should not be mixed with insulin zinc suspensions since the phosphate buffer may interact with the zinc in the suspension and alter the timing of action of the insulin in an unpredictable way.

Insulin preparations which have been frozen must not be used.

Insulin solutions should not be used if they do not appear water clear and colourless.

#### **Insulin infusion (CSII):**

Use only syringes made of polyethylene, polypropylene or glass.

Use only catheters where the material in contact with the insulin is made of polyethylene or polypropylene.

Use only teflon-coated or stainless steel needles.

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

## **7. MARKETING AUTHORISATION HOLDER**

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

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/02/232/001-003

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 07 October 2002

Date of latest renewal: 18 September 2007

**10. DATE OF REVISION OF THE TEXT**

Medicinal product no longer authorised

**ANNEX II**

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE  
SUBSTANCE AND MANUFACTURING AUTHORISATION  
HOLDERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

Medicinal product no longer authorised

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer of the biological active substance

Novo Nordisk A/S Novo Nordisk A/S  
Novo Allé Hallas Allé  
DK-2880 Bagsværd DK-4400 Kalundborg  
Denmark Denmark

Name and address of the manufacturers responsible for batch release

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

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

Medicinal product no longer authorised

Medicinal product no longer authorised

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

Medicinal product no longer authorised

**A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Velosulin 100 IU/ml solution for injection or infusion in a vial  
Insulin human (rDNA)

**2. STATEMENT OF ACTIVE SUBSTANCE**

1 ml solution contains 100 IU (3.5 mg) of insulin human (rDNA).

**3. LIST OF EXCIPIENTS**

zinc chloride, glycerol, metacresol, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid and water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection or infusion  
1 x 10 ml  
5 x 10 ml

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous or intravenous use  
Read the package leaflet before use

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

Keep out of the reach and sight of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP/  
During use: use within 6 weeks

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C - 8°C)

Do not freeze

Keep the vial in the outer carton in order to protect from light

During use: do not refrigerate or store above 25°C

May be kept in an infusion pump at up to 37°C for 6 days

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novo Nordisk A/S

Novo Allé

DK-2880 Bagsværd

Denmark

**12. MARKETING AUTHORISATION NUMBERS**

EU/1/02/232/001 1 x 10 ml

EU/1/02/232/002 5 x 10 ml

**13. BATCH NUMBER**

Batch:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Velosulin



**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Velosulin 100 IU/ml solution for injection or infusion  
Insulin human (rDNA)  
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**

Novo Nordisk A/S

Medicinal product no longer authorised

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Velosulin 100 IU/ml solution for injection or infusion in a vial  
Insulin human( rDNA)

**2. STATEMENT OF ACTIVE SUBSTANCE**

1 ml solution contains 100 IU (3.5 mg) of insulin human (rDNA).

**3. LIST OF EXCIPIENTS**

zinc chloride, glycerol, metacresol, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid and water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection or infusion  
1 x 10 ml  
This is part of a multipack and not for sale of individual vials

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous or intravenous use  
Read the package leaflet before use

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

Keep out of the reach and sight of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP/  
During use: use within 6 weeks

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C - 8°C)

Do not freeze

Keep the vial in the outer carton in order to protect from light

During use: do not refrigerate or store above 25°C

May be kept in an infusion pump at up to 37°C for 6 days

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

**12. MARKETING AUTHORISATION NUMBERS**

EU/1/02/232/003

**13. BATCH NUMBER**

Batch:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Velosulin

**PARTICULARS TO APPEAR ON THE PACKAGING**

**OUTER WRAPPER LABEL ON MULTIPACKS**

**1. NAME OF THE MEDICINAL PRODUCT**

Velosulin 100 IU/ml Solution for injection or infusion in a vial  
Insulin human (rDNA)

**2. STATEMENT OF ACTIVE SUBSTANCE**

1 ml solution contains 100 IU (3.5 mg) of insulin human (rDNA).

**3. LIST OF EXCIPIENTS**

zinc chloride, glycerol, metacresol, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid and water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection or infusion  
5 x (1 x 10 ml)  
This is a multipack and not for sale of individual vials

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous or intravenous use  
Read the package leaflet before use

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

Keep out of the reach and sight of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP/  
During use: use within 6 weeks

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C - 8°C)

Do not freeze

Keep the vial in the outer carton in order to protect from light

During use: do not refrigerate or store above 25°C

May be kept in an infusion pump at up to 37°C for 6 days

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/02/232/003

**13. BATCH NUMBER**

Batch:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Medicinal product no longer authorised

**B. PACKAGE LEAFLET**

## PACKAGE LEAFLET: INFORMATION FOR THE USER

### Velosulin 100 IU/ml solution for injection in a vial Insulin human (rDNA)

**Read all of this leaflet carefully before you start using your insulin.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, diabetes nurse or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, diabetes nurse or your pharmacist.

#### 1. WHAT VELOSULIN IS AND WHAT IT IS USED FOR

**Velosulin is human insulin to treat diabetes.** Velosulin is a fast-acting insulin. This means that it will start to lower your blood sugar about half an hour after you take it.

#### 2. BEFORE YOU USE VELOSULIN

##### Do not use Velosulin

- ▶ **If you are allergic (hypersensitive)** to this insulin product, metacresol or any of the other ingredients (see 7 *Further information*). Look out for the signs of allergy in 5 *Possible side effects*
- ▶ **If you feel a hypo** coming on (a hypo is short for a hypoglycaemic reaction and is a symptom of low blood sugar). See 4 *What to do in an emergency* for more about hypos.

##### Take special care with Velosulin

- ▶ **If you have trouble** with your kidneys or liver, or with your adrenal, pituitary or thyroid glands
- ▶ **If you are drinking alcohol:** watch for signs of a hypo and never drink alcohol on an empty stomach
- ▶ **If you are exercising** more than usual or if you want to change your usual diet
- ▶ **If you are ill:** carry on taking your insulin
- ▶ **If you are going abroad:** travelling over time zones may affect your insulin needs and the timing of your injections.

##### Using other medicines

Many medicines affect the way glucose works in your body and they may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment. Talk to your doctor or pharmacist if you take or have recently taken any other medicines, even those not prescribed.

**Your need for insulin may change** if you also take: oral antidiabetic products; monoamine oxidase inhibitors (MAOI); beta-blockers; ACE-inhibitors; acetylsalicylic acid; anabolic steroids; sulphonamides; oral contraceptives; thiazides; glucocorticoids; thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide or lanreotide.

##### Pregnancy and breast-feeding

**If you are pregnant, planning a pregnancy or breast-feeding:** please contact your doctor for advice.

## Driving and using machines

**If you drive or use tools or machines:** watch out for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on. Discuss with your doctor whether you can drive or use machines at all, if you have a lot of hypos or if you find it hard to recognise hypos.

## 3. HOW TO USE VELOSULIN

Talk about your insulin needs with your doctor and diabetes nurse. Follow their advice carefully. This leaflet is a general guide.

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.

Eat a meal or snack containing carbohydrates within 30 minutes of administration.

It is recommended that you measure your blood glucose regularly.

### Before using Velosulin

- ▶ **Check the label to make sure** it is the right type of insulin
- ▶ **Disinfect the rubber membrane** with a medicinal swab.

### Do not use Velosulin

- ▶ **If the protective cap is loose or missing.** Each vial has a protective, tamper-proof plastic cap. If it isn't in perfect condition when you get the vial, return the vial to your supplier
- ▶ **If it hasn't been stored correctly** or been frozen (see 6 *How to store Velosulin*)
- ▶ **If it does not appear water clear and colourless.**

### Use in infusion pump

Follow the instructions and recommendations from your doctor regarding the use of Velosulin in a pump.

Velosulin should never be mixed with any other insulin when used in a pump.

Read and follow carefully the instructions that accompany your insulin pump.

Always have ordinary syringes available in case of pump interruption or failure.

### Use in syringes

Velosulin is for injection under the skin (subcutaneously). Always vary the sites you inject, to avoid lumps (see 5 *Possible side effects*). The best places to give yourself an injection are: the front of your waist (abdomen); your buttocks; the front of your thighs or upper arms. Your insulin will work more quickly if you inject it around the waist.

Velosulin vials are for use with insulin syringes with the corresponding unit scale.

Velosulin may also be administered intravenously in special situations by medical professionals.

### To inject Velosulin on its own

1. Draw air into the syringe, in the same amount as the dose of insulin you need
2. Inject the air into the vial: push the needle through the rubber stopper and press the plunger
3. Turn the vial and syringe upside down
4. Draw the right dose of insulin into the syringe
5. Pull the needle out of the vial
6. Make sure there is no air left in the syringe: point the needle upwards and push the air out
7. Check you have the right dose



8. Inject the insulin straight away under the skin. Use the injection technique advised by your doctor or diabetes nurse
9. Keep the needle under your skin for at least 6 seconds to make sure that the full dose has been delivered.

### **To mix Velosulin with long acting insulin**

Follow the instructions of your doctor or diabetes nurse concerning the correct mixing procedure.

## **4. WHAT TO DO IN AN EMERGENCY**

### **If you get a hypo**

A hypo means your blood sugar level is too low.

**The warning signs of a hypo** may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

**If you get any of these signs**, eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.

**Don't take any insulin** if you feel a hypo coming on.

Carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

**Tell your relatives, friends and close colleagues** that if you pass out (become unconscious), they must: turn you on your side and seek medical advice straight away. They must not give you any food or drink as it could choke you.

- ▶ **If severe hypoglycaemia** is not treated, it can cause brain damage (temporary or permanent) and even death
- ▶ **If you have a hypo** that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

### **Using glucagon**

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 sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Seek medical advice after an injection of glucagon; you need to find the reason for your hypo to avoid getting more.

### **Causes of a hypo**

You get a hypo if your blood sugar gets too low. This might happen:

- If you take too much insulin
- If you eat too little or miss a meal
- If you exercise more than usual.

### **If your blood sugar gets too high**

Your blood sugar may get too high (this is called hyperglycaemia).

**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.

**If you get any of these signs**, test your blood sugar level and test your urine for ketones if you can. Then seek medical advice straight away.

These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

## Causes of hyperglycaemia

- Having forgotten to take your insulin
- Repeatedly taking less insulin than you need
- An infection or a fever
- Eating more than usual
- Less exercise than usual.

## 5. POSSIBLE SIDE EFFECTS

Like all medicines, Velosulin can cause side effects, although not everybody gets them. Velosulin may cause hypoglycaemia (low blood sugar). See the advice in 4 *What to do in an emergency*.

**Side effects reported uncommonly** (in less than 1 patient in 100)

**Vision problems.** When you first start your treatment, it may disturb your vision, but the reaction usually disappears.

**Changes at the injection site (Lipodystrophy).** If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to prevent such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or diabetes nurse because these reactions can become more severe, or they may change the absorption of your insulin if you inject in such a site.

**Signs of allergy.** Reactions (redness, swelling, itching) at the injection site may occur (local allergic reactions). These usually disappear after a few weeks of taking your insulin. If they do not disappear, see your doctor.

**Seek medical advice immediately:**

- if signs of allergy spread to other parts of the body, or
- if you suddenly feel unwell and you start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy; feel like fainting.

**You may have a very rare serious allergic reaction** to Velosulin or one of its ingredients (called a systemic allergic reaction). See also warning in 2 *Before you use Velosulin*.

**Painful neuropathy** (nerve related pain). If your blood glucose levels improve very fast it may cause a burning, tingling or electric pain. This is called acute painful neuropathy and it usually disappears. If it does not disappear, see your doctor.

**Swollen joints.** When you start taking insulin, water retention may cause swelling around your ankles and other joints. This soon disappears.

**Side effects reported very rarely** (in less than 1 patient in 10,000)

**Diabetic retinopathy** (eye background changes). If you have diabetic retinopathy and your blood glucose levels improve very fast, the retinopathy may get worse. Ask your doctor about this.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, diabetes nurse or pharmacist.

## 6 HOW TO STORE VELOSULIN

Keep out of the reach and sight of children.

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

**The vials that is not being used** is to be stored in a refrigerator (2°C - 8°C).

Do not store them in or too near the freezer section or cooling element.

Do not freeze.

Keep the vials in the original package.

**The vials that are being used** or about to be used is not to be kept in a refrigerator. You can keep it in the pump reservoir for 6 days at up to 37°C (close to the body). The vial may be kept at room temperature (not above 25°C) for 6 weeks after first opening.

Always keep the vial in the outer carton when you're not using it in order to protect it from light.

Velosulin must be protected from excessive heat and sunlight.

Velosulin should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 7. FURTHER INFORMATION

### What Velosulin contains

- **The active substance** is insulin human made by recombinant biotechnology. 1 ml contains 100 IU of insulin human. 1 vial contains 10 ml equivalent to 1000 IU
- **The other ingredients are** zinc chloride, glycerol, metacresol, disodium phosphate dihydrate, sodium hydroxide, hydrochloric acid and water for injections.

### What Velosulin looks like and contents of the pack

The solution for injection or infusion comes as a clear, colourless, aqueous solution.

It is supplied in packs of 1 or 5 vials of 10 ml or in a multipack of 5 x (1 x 10 ml) vials. Not all packs may be marketed.

### Marketing Authorisation Holder and Manufacturer

Novo Nordisk A/S

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