Insuman® Comb 25 100 IU/ml

Hoechst Marion Roussel

This package insert is continually updated: please read carefully before using a new pack!

Insuman® Comb 25 100 IU/ml

Active ingredient: Insulin human

Insulin with a gradual onset and long duration of action

Composition

Each ml of the neutral injection suspension contains 100 IU (U 100) of insulin human (25% dissolved insulin, 75% crystalline protamine insulin).

Excipients: Protamine sulphate, m-cresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid, water for injections.

Properties

Insuman Comb 25 is an antidiabetic which contains insulin manufactured by recombinant DNA technology and identical with the body's own insulin. The effect of Insuman Comb 25 sets in within 30 to 60 minutes, reaches its maximum within 2 to 4 hours after injection, and lasts for 12 to 19 hours. Insuman Comb 25 may be mixed with all Hoechst Marion Roussel human insulins except for that designed specifically for use in insulin pumps (Insuman Infusat).

Indication

Insulin-dependent diabetes mellitus.

Contraindications

Hypersensitivity to any of the product's components (see "Composition"), except where treatment is essential and no better tolerated insulin preparation is available. In such cases, administration of Insuman Comb 25 must only be continued under close medical supervision and, if necessary, in conjunction with concomitant anti-allergic treatment.

Insuman Comb 25 must not be used where an excessive reduction in blood sugar (hypoglycaemia) is present or menacing.

Special warnings and precautions

Where patients hypersensitive to animal insulin are to be changed to Insuman Comb 25, consideration must be given to the possibility of an immunological cross-reaction between animal and human insulin. In such patients, intradermal skin testing should be carried out before starting treatment.

Hypoglycaemia may occur if more insulin than needed is injected. Possible signs and symptoms of a low sugar level in the brain include: headache, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, impaired concentration and reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesiae), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after oneself, delirium, convulsions, somnolence, loss of consciousness up to and including coma, shallow breathing, slow heart rate (bradycardia). The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke. Most well-controlled patients may experience episodes of hypoglycaemia in mild form without conspicuous symptoms.

In many patients, the signs and symptoms of a low sugar level in the brain are preceded by adrenergic counter-regulation which is manifested in such bodily signs and symptoms as: sweating, clammy skin, anxiety, rapid heart rate (tachycardia), high blood pressure, palpitations, chest pain (angina pectoris), irregular heart beat (cardiac arrhythmias).

Patients must learn to recognise the signs and symptoms of hypoglycaemia and the measures for corrective action. Patients with weak or absent adrenergic warning symptoms must be specifically trained to recognise the symptoms of low sugar level in the brain at an early stage. Patients not confident of recognising the warning symptoms of hypoglycaemia should avoid situations that might result in danger to themselves or others. Patients who check their blood and urine sugar frequently are at less risk of hypoglycaemic reactions.

In certain circumstances, the warning symptoms and signs of hypoglycaemia may change, be milder, or be absent. In such cases, patients may fail to take prompt corrective measures to keep blood sugar from dropping further. Their ability to cope with the situation and their state of consciousness may worsen rapidly. Such situations may occur in elderly patients, or in patients with a disorder of part of the nervous system (autonomic neuropathy), in those with a long history of diabetes, those with a psychiatric illness, those being treated concomitantly with other medicines (see "Interactions"), those in whom very low blood sugar levels are being targeted, and those who have just been changed to a different insulin preparation. Patients whose blood sugar control has improved markedly (e.g. through intensified insulin therapy) may lose some or all of the warning signs of hypoglycaemia, and may therefore slip into sometimes severe hypoglycaemia with loss of consciousness, without realising it as early and as clearly as before and without having the opportunity to take corrective action.

A large number of factors increase the susceptibility to hypoglycaemia. These include:

- inappropriate insulin dosage regimens, doses which are too high, errors in administration
- lack of compliance (particularly in the elderly: inability to comply)
- missed meals, smaller than usual meals, changes in diet
- vomiting, diarrhoea
- consumption of alcohol (reduced gluconeogenesis), particularly in conjunction with fasting
- unaccustomed, increased or prolonged physical activity
- lack of or reduced awareness of the warning symptoms of hypoglycaemia

- improved insulin sensitivity, by, e.g., removal of stress factors
- impaired renal function (lower requirement due to reduced insulin breakdown). In the elderly, progressive deterioration of renal function may lead to a steady decrease in the insulin requirements
- severe impairment of liver function (reduced capacity for gluconeogenesis, reduced insulin breakdown entailing lower insulin requirement)
- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycaemia (as, for example, in reduced thyroid function and in anterior pituitary or adrenocortical insufficiency)
- concurrent administration of other medicines with a blood-sugar-lowering action (see "Interactions")
- change in the injection area (differences in absorption).

The doctor must be informed of such factors since these may require particularly close monitoring and may necessitate dose adjustment.

The risk of hypoglycaemia is high at the start of insulin treatment, following transfer to a different insulin preparation, in patients with close to normal hypoglycaemic control, and in patients with marked fluctuations in blood sugar levels.

The likelihood of hypoglycaemia is also increased in patients with a history of severe hypoglycaemic episodes.

A mild hypoglycaemic attack can be corrected by taking sugar, e.g., in the form of glucose, sugar cubes or sugar-sweetened beverages. Patients should always carry at least 20 grams of glucose with them for this purpose (food or beverages containing artificial sweeteners – such as diet foods or drinks – are ineffective in controlling hypoglycaemia). After recovering sufficiently, some food having a long-acting blood-sugar-raising effect (e.g. bread) should be taken. If hypoglycaemia recurs, another 10 to 20 g of sugar should be taken. More serious hypoglycaemic reactions may require intravenous administration of glucose solution or glucagon. If a hypoglycaemic attack cannot be immediately corrected, a doctor should be called urgently. Every hypoglycaemic episode should be reported to the doctor, who will then decide whether to adjust therapy.

Patients in whom hypoglycaemic episodes might be of particular clinical relevance include those with significant narrowing of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia), or those with a certain eye disease (proliferative retinopathy), particularly when not treated with a laser (risk of post-hypoglycaemic blindness). Particular caution should be exercised and intensified blood sugar monitoring is advisable in such patients.

Incorrect diet, omission or reduction of insulin injections, or increased insulin requirements during infections or other diseases and circumstances (e.g. decreased physical activity) may lead to an increase in blood sugar levels **(hyperglycaemia)**, possibly with an accumulation of ketone bodies in the blood (ketoacidosis). Depending on the amount of insulin available, ketoacidosis may develop within hours or days. At the first signs of a deterioration in metabolic control (thirst, large urine volumes, loss of appetite, tiredness, dry skin, rapid and deep breathing, and high glucose and acetone concentrations in the urine), medical aid must be sought immediately.

Please inform your doctor in the event of intercurrent illness, since this situation necessitates intensified metabolic monitoring and, possibly, further special measures (e.g., dose adjustment, urine tests for ketones). If you are treated by a different doctor (upon, e.g., admission to hospital after an accident, illness while on holiday), you must tell the new doctor about your diabetes.

Hypoglycaemia may impair the ability to concentrate and react and therefore constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery).

Pregnancy and lactation

Treatment with Insuman Comb 25 must be continued during pregnancy. In the first three months, insulin requirements usually decrease, but they increase thereafter. Immediately after delivery, they then decrease again rapidly (increased risk of hypoglycaemia). Therefore, careful monitoring of blood sugar and the general condition is essential. If you are pregnant or are planning pregnancy, please inform your doctor.

There is no restriction on treatment with Insuman Comb 25 during lactation. However, adjustments in dosage and diet may be necessary.

Adverse effects

Hypoglycaemia may develop if the insulin dose exceeds requirements (see "Special warnings and precautions").

A marked change in blood sugar level may cause temporary visual impairment. Also, intensified insulin therapy with improved blood sugar control may lead temporarily to a worsening of diabetic retinopathy; overall, however, such improved control decreases the risk of its progression. In patients with proliferative retinopathy, particularly when not treated with a laser, severe hypoglycaemic attacks may cause blindness.

Fatty tissue under the skin may shrink or swell (lipoatrophy or lipohypertrophy) at the injection site and delay insulin absorption and its effect. Selecting a different site for each injection may help to reduce or prevent these reactions. Mild and transient reddening may occur at the injection site.

In rare cases, local immediate-type or delayed-type hypersensitivity reactions (e.g. Arthus reactions) to insulin or to any of the excipients may occur. They may manifest themselves as itching, wheals, reddening, hardening or lumps in or under the skin, or unusual intense pain at the injection site, and may also spread into the area around the injection site. Severe hypersensitivity reactions, however, are very rare. Such reactions may be accompanied, e.g., by skin rashes, skin and mucosal swellings (angio-oedema), shortness of breath (bronchospasm), drop in blood pressure and circulatory collapse (shock). Hypersensitivity reactions may necessitate a change in insulin preparation or adjunctive therapy (see "Contraindications").

Antibodies to insulin may form and such formation may, in rare cases, necessitate dose adjustment. Insulin may cause sodium retention and a build-up of fluid in the tissues (oedema), particularly after intensified therapy.

A potassium deficiency state (hypokalaemia) with, e.g., cardiac complica-

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tions, or cerebral oedema may develop as a consequence of marked acute blood sugar lowering.

Please speak with your doctor if you notice any of the adverse effects listed in this package insert or any other undesired effects or unexpected changes.

Since some adverse effects (e.g., severe hypoglycaemia, severe hypersensitivity reactions) may under certain circumstances become life-threatening, it is essential that, if sudden or severe reactions do occur, you inform a doctor at once.

Interactions

Concomitant administration of certain other medicines may either weaken or potentiate the blood-sugar-lowering action of Insuman Comb 25. Therefore, other medicines may only be used with the doctor's consent during insulin treatment.

Hypoglycaemic reactions due to potentiation of the insulin effect may occur if patients are simultaneously treated with ACE inhibitors, acetylsalicylic acid and other salicylates such as para-aminosalicylic acid (especially at higher doses; in toxic doses, however, it has a blood-sugar-raising effect), amphetamines, anabolic steroids and male sex hormones, cibenzoline, cyclophosphamide, disopyramide, fenfluramine, fibrates, fluoxetine, guanethidine, ifosfamide, MAO inhibitors, oral antidiabetics, pentoxifylline, perhexiline, phenoxybenzamine, phentolamine, propoxyphene, somatostatin and its analogues, sulfonamide antibiotics, tetracyclines, tritoqualine, or trofosfamide.

A weakening of the insulin effect and, thereby, a worsening of the metabolic condition, may occur if insulin is administered to patients treated with ACTH (corticotrophin), barbiturates, corticosteroids, danazol, diazoxide, diuretics, doxazosin, glucagon, heparin, isoniazid, laxatives (including phenolphthalein) after prolonged use, nicotinic acid in high doses, oestrogens and progestogens, phenothiazines, phenytoin, prazosin, somatropin, sympathomimetic agents (epinephrine [adrenaline], salbutamol, terbutaline, and others), or thyroid hormones.

Clonidine, reserpine, or lithium salts may either potentiate or weaken the blood-sugar-lowering action of insulin. Pentamidine may cause hypoglycaemia, sometimes followed by hyperglycaemia.

Beta-blockers may increase the blood sugar level and worsen metabolic control. In addition, due to impaired counter-regulation, they increase the tendency to hypoglycaemia, and – in common with other sympatholytic medicines (e.g., clonidine, guanethidine, reserpine) – may weaken or even suppress entirely the warning symptoms of a hypoglycaemic reaction.

Alcohol may increase the blood sugar level; large amounts may increase the likelihood and intensity of hypoglycaemia. Consideration must also be given to the carbohydrate content of alcoholic beverages.

Dosage

On the basis of diet, physical activity and life-style, the doctor will determine and adjust for each patient individually the desired blood sugar level as well as dosage and injection schedule. Individual doses are based on the results of blood sugar measurements as well as on planned activity and carbohydrate intake. Insulin therapy generally requires appropriate patient education and self-monitoring. The doctor will give guidance on how often blood sugar measurements and – possibly – urine tests are to be performed, and also on what to do in case of, e.g., deviations from prescribed dosage regimen or missed meals.

There are no fixed rules for insulin dosage. However, the average daily requirement is often 0.5 to 1.0 IU per kg body weight, 40% to 60% of which is the basal requirement.

When changing from animal to human insulin, it may be necessary to reduce the dose. An adjustment may also be necessary when changing from other insulins to this preparation. Particularly frequent metabolic monitoring is necessary during changeover and in the initial weeks thereafter.

Improved metabolic control may result in increased insulin sensitivity leading to a reduced insulin requirement. Dose adjustments may also be required in conjunction with, e.g., weight or lifestyle changes, other circumstances which may promote increased susceptibility to hypo- or hyperglycaemia or intercurrent illness (see "Special warnings and precautions").

Administration

Generally, Insuman Comb 25 is given by deep subcutaneous injection 30 to 45 minutes before a meal, but also may be injected intramuscularly. A different site should be chosen for each injection. However, a change in injection area, e.g., from the abdominal wall to the thigh, should only be made after speaking with your doctor.

Insuman Comb 25 is not suited for use in external or implanted insulin pumps.

Never inject Insuman Comb 25 intravenously.

Do not mix Insuman Comb 25 with insulins of a different strength (e.g. 100 IU with 40 IU per ml), with animal-source insulins, or with any other medicines.

The vial contains insulin in a concentration of **100 IU/ml (U 100)**. Only plastic syringes designed for **this strength** may be used. Syringes must not contain any other medicines or traces thereof.

Before the first withdrawal of insulin from the vial, remove and discard the safety tear-off lid. Mix the suspension thoroughly immediately prior to drawing. This is best done by rolling the vial at an oblique angle between the palms of both hands. Do not shake the vial vigorously as this may lead to changes in the suspension (see below) and may cause froth to form, making correct dosage measurement difficult. After mixing, the suspension must have a uniformly milky-white appearance. Do not use the suspension if this cannot be achieved, i.e., if it remains clear, for example, or if clumps, particles, or flocculation are visible in the vial, or sticking to the sides or at the bottom. These changes sometimes give the vial a frosted appearance. In such cases, and also where the insulin requirement changes substantially, use a new vial yielding a uniform suspension and inform your doctor or pharmacist.

Upon obtaining the uniform suspension, inject an amount of air corresponding to the prescribed dose into the vial (but not into the liquid). Invert the vial with the syringe and draw the required amount of insulin into the syringe. Remove any air bubbles before injection. Take care to ensure that no alcohol or other disinfectant contaminates the insulin. Form a fold of

skin at the injection site, then insert the needle and slowly inject the insulin. After injection, slowly withdraw the needle and press a pad slightly to the puncture site for a few seconds.
The date of the first withdrawal from the vial should be noted on the label. Once opened, the vial may be used for up to four weeks when stored below 25 °C and protected from direct heat and light.

Overdose
Insulin overdose may lead to severe and sometimes life-threatening hypoglycaemia. Patients who are still conscious must immediately take sugar followed by long-acting carbohydrates (see "Special warnings and precautions"). Patients having lost consciousness and who have not consumed large amounts of alcohol are administered 1 mg of glucagon intramuscularly. Alternatively, or if the glucagon injection fails to restore metabolic control immediately, adults may be administered 20–30 ml of a 30 % to 50 % glucose solution intravenously. This dose may be repeated if necessary. In children, the dose is reduced in proportion to body weight.
Severe or prolonged hypoglycaemia generally necessitates that glucagon injection and/or acute glucose administration be followed up by infusion of a less concentrated glucose solution (while monitoring the blood sugar level) to prevent recurrence of hypoglycaemia. In addition, glucagon administration (intramuscular or subcutaneous) may be repeated. Due to the possible risk of severe hyperglycaemia, glucose must be administered in young children with extreme caution, while very closely monitoring blood sugar levels.
Patients, once having regained consciousness, are given long-acting carbohydrates for oral intake to prevent relapse. Careful monitoring is required until the patient can be assumed to be out of danger. In certain circumstances, hospitalisation (even as a precautionary measure) may be required, and monitoring and treatment in the intensive care unit may become necessary.

Storage
Store at +2 °C to +8 °C. Do not freeze. Avoid direct contact of the vial with freezer compartment or freezer packs.

Expiry date
Do not use later than the date of expiry.

Keep medicines out of the reach of children.

Presentation
Suspension for injection
1 vial containing 5 ml (500 IU)
5 vials, each containing 5 ml (500 IU)