For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack.

INSUMAN® RAPID
Human Insulin Injection I.P.
100 IU/mL in 3mL Cartridges (for use with Allstar)

INSUMAN® COMB 25
Biphasic Isophane Insulin Injection I.P.
100 IU/mL in 3mL Cartridges (for use with Allstar)

INSUMAN® COMB 50
Biphasic Isophane Insulin Injection I.P.
100 IU/mL in 3mL Cartridges (for use with Allstar)

Monocomponent Insulin Recombinant DNA Origin

Therapeutic Class
Antidiabetic agent

Pharmaceutical Form
Cartridges

Composition
The human insulin in Insuman is produced by recombinant DNA technology using K 12 strains of *Escherichia coli.*

- **Insuman Rapid**
  Insuman Rapid is a neutral insulin solution (regular insulin)

- **Insuman Mixed**
  Insuman Comb 25 : is biphasic isophane insulin suspension (25% dissolved insulin + 75% crystalline protamine insulin)

  Insuman Comb 50 : is biphasic isophane insulin suspension (50% dissolved insulin + 50% crystalline protamine insulin).

For Cartridges
Each ml of Insuman contains 100IU of insulin human. Each cartridge contains 3 ml, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Indication
For the treatment of type 1 or type 2 diabetes mellitus.

Dosage and Administration

General
The desired blood glucose levels, the insulin preparations to be used and the insulin dosage (doses and timings) must be determined and adjusted individually to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dosage. However, the average insulin requirement is often 0.5 to 1.0 I.U. per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement.

- **Insuman Rapid** is injected subcutaneously approximately 15 to 20 minutes before a meal.
- **Insuman Mixed**
    - **Insuman Comb 25** is injected subcutaneously approximately 30 to 45 minutes before a meal.
    - **Insuman Comb 50** is injected subcutaneously approximately 20 to 30 minutes before a meal.

Applies Insuman Rapid only:
In the treatment of severe hyperglycaemia or ketoacidosis in particular, insulin administration is part of a complex therapeutic regimen, which includes measures to protect patients from possible severe complications of a relatively rapid lowering of blood glucose. This regimen requires close monitoring (metabolic status, acid-base and electrolyte status, vital parameters etc.) in an intensive care unit or similar setting.

Transfer to Insuman

Dosage adjustment may be necessary when transferring patients from one insulin preparation to another. This applies, for example, when transferring from:
- an animal insulin (especially a bovine insulin) to human insulin
- one human insulin preparation to another
- a regimen with only regular insulin to one with a longer-acting insulin

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dosage reduction may be required in particular in patients who:
- were previously already controlled on rather low blood glucose levels
- have a tendency to hypoglycaemia
- previously required high insulin doses due to the presence of insulin antibodies

Close metabolic monitoring is recommended during transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if:
- the patient's weight changes
- the patient's life-style changes

- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see Precautions)

SPECIAL POPULATIONS

Elderly
In the elderly, insulin requirements may be diminished (see Precautions). In elderly patients with diabetes, it is recommended that the initial dosing, dose increments, and maintenance dosage be conservative to avoid hypoglycaemic reactions. Hypoglycaemia may be difficult to recognise in the elderly (see Precautions).

Hepatic impairment
In patients with hepatic or renal impairment, insulin requirements may be diminished (see Precautions).

Renal impairment
In patients with hepatic or renal impairment, insulin requirements may be diminished (see Precautions).

ADMINISTRATION

Insuman is administered subcutaneously.
Insulin absorption and hence the blood glucose lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next.

Insuman Mixed (Insuman Comb 25 and Insuman Comb 50) must never be injected intravenously.

Insuman Rapid:
Insuman Rapid may also be administered intravenously. Intravenous insulin therapy must generally take place in a hospital setting or under comparable monitoring and treatment conditions.

For Cartridges:
Insuman in cartridges has been developed for use with AllStar (see instruction leaflet for the insulin pen).

Mixing of insulins
Insuman may be mixed with all sanofi human insulins. Insuman must not be mixed with insulin designed specifically for use in insulin pumps. Insuman must also not be mixed with insulins of animal origin or with insulin analogues.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Insuman Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.
- Insuman Mixed must not be administered intravenously and must not be used in infusion pump or external/implanted insulin pumps.

PRECAUTIONS
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism. In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

As with all insulins, particular caution should be exercised and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia), as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or absent, for example:
- if glycaemic control is markedly improved
- if hypoglycaemia develops gradually
- in elderly patients
- in patients with autonomic neuropathy
- in patients with a long history of diabetes
- in patients receiving concurrent treatment with certain other medicinal products (see interactions)

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient’s awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dosage and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area
- improved insulin sensitivity (by, e.g., removal of stress factors)
- unaccustomed, increased or prolonged physical activity
- intercurrent illness (e.g. vomiting, diarrhoea)
- inadequate food intake
- missed meals
- alcohol consumption
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency)
- concomitant treatment with certain other medicinal products

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Pens to be used with Insuman cartridges
The Insuman cartridges should only be used with AllStar and should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

INTERACTIONS
A number of substances affect glucose metabolism and may require dose adjustment of human insulin. Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic agents, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine, salbutamol, terbutaline) and thyroid hormones.

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood glucose lowering effect of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

PREGNANCY
There is no experience with the use of Insuman in pregnant women. Insulin does not cross the placental barrier.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy.

Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

LACTATION
Lactating women may require adjustments in insulin dose and diet.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. 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 symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

ADVERSE REACTIONS

Hypoglycaemia, in general the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological events,including coma and seizures (see also Overdose section). Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Medication errors have been reported in which other Insuman formulations or other insulins have been accidentally administered.

The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders

Immediate-type allergic reactions to insulin or to the excipients (frequency not known) may, for example, be associated with generalised skin reactions (frequency not known), angioneurotic oedema(frequency not known), bronchospasm (frequency not known), hypotension (frequency not known) and shock (uncommon), and may be life-threatening.

Insulin administration may cause insulin antibodies to form (frequency not known). 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.

Metabolism and nutrition disorders

Insulin may cause sodium retention (frequency not known) and oedema (common), particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment (frequency not known) due to temporary alteration in the turgidity and refractive index of the lens. 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 (frequency not known). In patients with proliferative retinopathy (frequency not known), particularly if not treated with photocoagulation, severe hypoglycaemic episodes may result in transient amaurosis.

Skin and subcutaneous tissue disorders

As with any insulin therapy, lipodystrophy (frequency not known) 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.

General disorders and administration site conditions

Mild reactions at the injection site may occur commonly. Such reactions include injection site erythema (frequency not known), injection site pain (frequency not known), injection site pruritus (frequency not known), injection site urticaria (frequency not known), injection site

swelling (frequency not known), or inflammation (frequency not known). Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

OVERDOSE

SIGNS AND SYMPTOMS
Symptoms
Insulin overdose, e.g. an excess of insulin relative to food intake/energy expenditure, may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

MANAGEMENT
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dosage of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

INTERFERENCES WITH LABORATORY AND DIAGNOSTIC TEST
None known

ABUSE AND DEPENDENCE
No risk of abuse or dependence is likely to occur with Insuman.

INCOMPATIBILITIES / COMPATIBILITIES
Concerning miscibility or incompatibility with other insulins see Dosage and Administration. Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

As with all insulin preparations, Insuman must not be mixed with solutions containing reducing agents such as thioles and sulfites.

Regular insulin prescipitates out at a pH of approximately 4.5 to 6.5.
Insulin protamine crystals dissolve in an acid pH range.

STORAGE CONDITIONS AND SHELF LIFE
Storage
Store at 2°C - 8°C. Keep the container in the outer carton. Do not freeze. Ensure that the container is not directly touching the freezer compartment or freezer packs. Once in use, do not store above 25°C and protect from direct heat or light.

For cartridges:
When in use in the AllStar do not store in a refrigerator.

Shelf life
2 years

Cartridges
Once in use, the cartridge may be kept for up to four weeks (28 days). This applies irrespective of whether the cartridges is immediately put into the AllStar or is first carried as a spare for a while.

PREPARATION AND HANDLING

Insuman Rapid Cartridges
Before insertion into the AllStar, Insuman Rapid must be stored at room temperature for 1 to 2 hours. Insuman Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency.

Insuman Mixed Cartridges
Before insertion into the AllStar, Insuman Mixed must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the cartridge back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents.

Later on, when the cartridge has been inserted into the AllStar, the insulin must be resuspended again prior to each injection. This is best done by gently tilting the AllStar back and forth (at least ten times).

After resuspension, the fluid must have a uniformly milky appearance. Insuman Mixed must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new cartridge yielding a uniform suspension must be used. It is also necessary to change to a new cartridge if the insulin requirement changes substantially.

For Cartridges
Air bubbles must be removed from the cartridge before injection (see instructions for using the AllStar). The instructions for using the AllStar must be followed carefully. Empty cartridges must not be refilled.
Insuman cartridges are not designed to allow any other insulin to be mixed in the cartridge.

If the AllStar malfunctions, the suspension may be drawn from the cartridge into a syringe (suitable for an insulin with 100 IU/ml) and injected.

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