1. NAME OF THE MEDICINAL PRODUCT

Insuman Rapid 100 IU/ml solution for injection in a cartridge
Insuman Rapid 100 IU/ml solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge or pen contains 3 ml of solution for injection, equivalent to 300 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insuman Rapid is a neutral insulin solution (regular insulin).

Human insulin is produced by recombinant DNA technology in Escherichia coli.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a cartridge or pre-filled pen. (OptiSet).

Clear, colourless solution of water-like consistency.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

Cartridges: Insuman Rapid is also suitable for the treatment of hyperglycaemic coma and ketoacidosis, as well as for achieving pre-, intra- and post-operative stabilisation in patients with diabetes mellitus.

4.2 Posology and method of administration

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

Daily doses and timing of administration

There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insuman Rapid is injected subcutaneously 15 to 20 minutes before a meal.

OptiSet delivers insulin in increments of 2 IU up to a maximum single dose of 40 IU.

Cartridges: 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.

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 section 4.4).

Use in specific patient groups
In patients with hepatic or renal impairment as well as in the elderly, insulin requirements may be diminished (see section 4.4).

**Administration**

Insuman Rapid 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.

Before using OptiSet, the Instructions for Use included in the Package Leaflet must be read carefully.

**Cartridges:** Insuman Rapid may also be administered intravenously. Intravenous insulin therapy must generally take place in an intensive care unit or under comparable monitoring and treatment conditions (see "Daily doses and timing of administration").

For further details on handling, see section 6.6.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

**Cartridges:** Insuman Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.

### 4.4 Special warnings and precautions for use

Patients hypersensitive to Insuman Rapid for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insuman Rapid, since they may experience immunological cross-reactions.

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.

**Transfer to Insuman Rapid**

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dosage.

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, dose regimen 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 the 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.

**Hypoglycaemia**

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

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 be absent in certain risk groups. These include patients:

- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

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 dose regimen 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 (e.g. by 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.

**Medication errors**

Medication errors have been reported in which other Insuman formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

**Combination of Insuman 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 Insuman 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.

**Pens to be used with Insuman Rapid cartridges**
The Insuman Rapid cartridges should only be used with the following pens: OptiPen, ClikSTAR and Autopen 24 and should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

**Handling of the pen**
Before using OptiSet, the Instructions for Use included in the Package Leaflet must be read carefully. OptiSet has to be used as recommended in these Instructions for Use (see section 6.6).

**4.5 Interaction with other medicinal products and other forms of interaction**
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, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide 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 [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

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.

**4.6 Pregnancy and lactation**

**Pregnancy**
For insulin human, no clinical data on exposed pregnancies are available. Insulin does not cross the placental barrier. Caution should be exercised when prescribing to pregnant women.

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**
No effects on the suckling child are anticipated. Insuman Rapid can be used during breast-feeding.

Lactating women may require adjustments in insulin dose and diet.

**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 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 machines).
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 machines in these circumstances.

4.8 Undesirable effects

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. In clinical trials and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. 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.

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 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).

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

**Immune system disorders**

Uncommon: shock
Not known: immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions), anti-insulin antibodies

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

**Metabolism and nutrition disorders**

Common: oedema
Not known: sodium retention

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

**Eyes disorders**

Not known: proliferative retinopathy, diabetic retinopathy, visual impairment

A marked change in glycaemic control may cause temporary visual impairment, 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.

**Skin and subcutaneous tissue disorders**
Not known: lipodystrophy

As with any insulin therapy, lipodystrophy 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

Common: injection site reactions
Uncommon: injection site urticaria
Not known: injection site inflammation, injection site swelling, injection site pain, injection site pruritus, injection site erythema.

Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

4.9 Overdose

Symptoms
Insulin overdose 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 dose regimen 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Insulins and analogues for injection, fast-acting, ATC Code: A10AB01.

Mode of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic characteristics
Insuman Rapid is an insulin with rapid onset and short duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1 and 4 hours after injection and the duration of action is 7 to 9 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Local tolerability studies following subcutaneous and intramuscular administration in rabbits gave no remarkable findings. Studies of pharmacodynamic effects following subcutaneous administration in rabbits
and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Concerning mixing or incompatibility with other insulins see section 6.6. Care must be taken to ensure that no alcohol or other disinfectants enter the insulin solution.

6.3 Shelf life

2 years.

Shelf life after first use of the cartridge/pen:
The cartridge or pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.

Pens containing a cartridge and prefilled pens in-use must not be stored in the refrigerator.

The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened cartridges and not in-use pens:
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put InsuMan Rapid next to the freezer compartment or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In-use cartridges and pens:
For storage precautions, see section 6.3.

6.5 Nature and contents of container

3 ml solution in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).

Cartridges: The cartridges are sealed in a disposable pen injector. Injection needles are not included in the pack.

Packs of 5 cartridges or pens are available.

6.6 Special precautions for disposal and other handling

Cartridges:
The Insuman Rapid cartridges are to be used only in conjunction with OptiPen, ClikSTAR or Autopen 24 (see section 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer’s instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen malfunctions (see instructions for using the pen), the solution may be drawn from the cartridge into an injection syringe (suitable for an insulin with 100 IU/ml) and injected.

Before insertion into the pen, Insuman Rapid must be kept at room temperature for 1 to 2 hours.

Inspect the cartridge before use. 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.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

As with all insulin preparations, Insuman Rapid must not be mixed with solutions containing reducing agents such as thioles and sulphites. It must also be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Rapid may be mixed with all Sanofi-Aventis human insulins, but NOT with those designed specifically for use in insulin pumps. Insuman Rapid must also NOT be mixed with insulins of animal origin or with insulin analogues.

Insuman Rapid cartridges are not designed to allow any other insulin to be mixed in the cartridge.

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

OptiSet pens:
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.

Empty pens must never be re-used and must be properly discarded.

To prevent the possible transmission of disease, each pen must be used by one patient only.

As with all insulin preparations, Insuman Rapid must not be mixed with solutions containing reducing agents such as thioles and sulphites. It must also be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Rapid must not be mixed with any other insulin or with insulin analogues.
Any unused product or waste material should be disposed of in accordance with local requirements.

Handling of the pen The patient should be advised to read the instructions for use included in the package leaflet carefully before using OptiSet.

**Schematic diagram of the pen**

**Important information for use of OptiSet:**

- A new needle must always be attached before each use. Only needles that are compatible for use with OptiSet must be used.
- A safety test must always be performed before each injection.
- If a new OptiSet is used the initial safety test must be done with the 8 units preset by the manufacturer.
- The dosage selector can only be turned in one direction.
- The dosage selector (change the dose) must never be turned after injection button has been pulled out.
- This pen is only for the patients use. It must not be shared with anyone else.
- If the injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- OptiSet must never be used if it is damaged or if the patient is not sure if it is working properly.
- The patient must always have a spare OptiSet available in case the OptiSet is lost or damaged.

**Storage Instructions**

Please check section 6.4 of this SPC for instructions on how to store OptiSet.

If OptiSet is in cool storage, it should be taken out 1 to 2 hours before injection to allow it to warm up. Cold insulin is more painful to inject.

The used OptiSet must be discarded as required by your local authorities.

**Maintenance**

OptiSet has to be protected from dust and dirt.

The outside of the OptiSet can be cleaned by wiping it with a damp cloth.

The pen must not be soaked, washed or lubricated as this may damage it.

OptiSet is designed to work accurately and safely. It should be handled with care. The patient should avoid situations where OptiSet may be damaged. If the patient is concerned that the OptiSet may be damaged, he must use a new one.

**Step 1. Check the Insulin**

After removing the pen cap, the label on the pen and the insulin reservoir should be checked to make sure it contains the correct insulin.

The appearance of insulin should also be checked: the insulin solution must be clear, colourless, with no solid particles visible, and must have a water-like consistency.
Do not use this OptiSet if insulin is cloudy, coloured or has particles.

**Step 2. Attach the needle**

The needle should be carefully attached straight onto the pen.

**Step 3. Perform a safety test**

Prior to each injection a safety test has to be performed.

**For a new and unused OptiSet,** a dose of 8 units is already preset by the manufacturer for the first safety test.

**In-use OptiSet,** a dose of 2 units has to be selected by turning the dosage selector forward till the dose arrow points to 2. The dosage selector will only turn in one direction.

The injection button should be pulled out completely in order to load the dose. The dosage selector must never be turned after the injection button has been pulled out.

The outer and inner needle caps should be removed. The outer cap should be kept to remove the used needle.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed all the way in.

If insulin has been expelled through the needle tip, then the pen and the needle are working properly. If no insulin appears at the needle tip, step 3 should be repeated two more times until insulin appears at the needle tip. If still no insulin comes out, change the needle, as it might be blocked and try again. If no insulin comes out after changing the needle, the OptiSet may be damaged. This OptiSet must not be used.

**Step 4. Select the dose**

The dose can be set in steps of 2 units, from a minimum of 2 units to a maximum of 40 units. If a dose greater than 40 units is required, it should be given as two or more injections.

The patient must always check if he has enough insulin for the dose.

The residual insulin scale on the transparent insulin reservoir shows approximately how much insulin remains in the OptiSet. This scale must not be used to set the insulin dose.

If the black plunger is at the beginning of the coloured bar, then there are approximately 40 units of insulin available.

If the black plunger is at the end of the coloured bar, then there are approximately 20 units of insulin available.

The dosage selector should be turned forward until the dose arrow points to the required dose.

**Step 5. Load the dose**

The injection button should be pulled out as far as it will go in order to load the pen.

The patient must check if the selected dose is fully loaded. The injection button only goes out as far as the amount of insulin that is left in the reservoir.

The injection button allows checking the actual loaded dose. The injection button must be held out under tension during this check. The last thick line visible on the injection button shows the amount of insulin
loaded. When the injection button is held out only the top part of this thick line can be seen.

**Step 6. Inject the dose**

The patient should be informed on the injection technique by his health care professional. The needle should be inserted into the skin.

The injection button should be pressed all the way in. A clicking sound can be heard, which will stop when the injection button has been pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle from the skin. This ensures that the full dose of insulin has been delivered.

**Step 7. Remove and discard the needle**

The needle should be removed after each injection and discarded. This helps prevent contamination and/or infection as well as entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing. Needles must not be re-used.

The pen cap should be replaced on the pen.

**7. MARKETING AUTHORISATION HOLDER**

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

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

Cartridges: EU/1/97/030/030
OptiSet pens: EU/1/97/030/067

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

Date of first authorisation: 21 February 1997
Date of latest renewal: 21 February 2007

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

01 February 2011

**LEGAL CLASSIFICATION: POM**