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1. What Insuman Comb 50 is and what it is used for

Insuman Comb 50 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 50 is an insulin preparation with a rapid onset and moderately long duration of action. Insuman Comb 50 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. How Insuman Comb 50 Works

Insulin

- lowers blood glucose,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and liver,
- increases formation of fats (lipogenesis) in the liver and adipose tissue and inhibits break down of fats (lipolysis).

3. What you need to know before you use Insuman Comb 50

Do not use Insuman Comb 50

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 8).

Before you start to use it

Talk to your doctor, pharmacist or nurse before using Insuman Comb 50.

Follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor

Special patient groups

If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel

Before travelling, consult your doctor. You may need to talk about

- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries

In the following situations, the management of your diabetes may require a lot of care:

- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia). In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes

(insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

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

Other medicines and Insuman Comb 50

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dosage to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:

- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high

levels of blood lipids),
-monoamine oxidase (MAO) inhibitors (used to treat depression),
-pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
-sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:

-corticosteroids (such as "cortisone" used to treat inflammation),
-danazol (medicine acting on ovulation),
-diazoxide (used to treat high blood pressure),
-diuretics (used to treat high blood pressure or excessive fluid retention),
-glucagon (pancreas hormone used to treat severe hypoglycaemia),
-isoniazid (used to treat tuberculosis),
-oestrogens and progestogens (such as in the contraceptive pill used for birth control),
-phenothiazine derivatives (used to treat psychiatric disorders),
-somatropin (growth hormone),
-sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
-thyroid hormones (used to treat the thyroid gland disorders),
-protease inhibitors (used to treat HIV),
-atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:

-beta-blockers (used to treat high blood pressure),
-clonidine (used to treat high blood pressure),
-lithium salts (used to treat psychiatric disorders).
Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 50 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant.

Your insulin dosage may need to be changed during pregnancy and after giving birth.

Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

However, there is no experience with the use of Insuman Comb 50 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:

-you have hypoglycaemia (low blood sugar levels),
-you have hyperglycaemia (high blood sugar levels),
-you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:

-you have frequent episodes of hypoglycaemia,
-the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 50

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

4. How to use Insuman Comb 50

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar

(glucose) tests, your doctor will -determine how much Insuman Comb 50 per day you will need,
-tell you when to check your blood sugar level, and whether you need to carry out urine tests,
-tell you when you may need to inject a higher or lower dose of Insuman Comb 50.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. Ask your doctor for further information on *Hyperglycaemia and Hypoglycaemia*.

Frequency of administration

Insuman Comb 50 is injected

Comb 50 100 IU/ml Suspension for Injection in a vial
Insulin human

under the skin 20 to 30 minutes before a meal.

Method of administration

Insuman Comb 50 is a fluid (suspension) for injection under the skin. Do NOT inject Insuman Comb 50 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps – special insulin preparations are available for use in such devices.

How to handle the vials

Insuman Comb 50 contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off lid on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insuman Comb 50 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, the shorter-acting insulin be drawn first to prevent contamination of the vial by longer-acting preparation. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insuman Comb 50 than you should

-If you **have injected too much Insuman Comb 50**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar.

If you forget to use Insuman Comb 50

-If you **have missed a dose of**

Insuman Comb 50 or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently.
-Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 50

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 50 without speaking to a doctor, who will tell you what needs to be done.

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

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 50 and other insulins.

5. While You are Using Insuman Comb 50

Things you must do

Take Insuman Comb 50 according to your doctor's instructions.

Tell your doctor or pharmacist if you notice any of the side effects listed below or any other unwanted or unexpected effects.

Things you must not do

Do not stop taking Insuman Comb 50 unless advised by your doctor.

Things to be careful of

Please refer to your doctor before you take Insuman Comb 50.

6. Possible side effects

Like all medicines, this medicine can cause side effects, although

not everybody gets them.

The most frequent side effect is **hypoglycaemia (low blood sugar)**. The specific frequency cannot be estimated from available data (frequency not known). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angioedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Frequency of these reactions cannot be estimated from available data.

Side effects reported

commonly (may affect up to 1 in 10 people)

- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.

- Injection site reactions

Side effects reported

uncommonly (may affect up to 1 in 100 people)

- Severe allergic reaction with low blood pressure (shock)
- Injection site urticaria (itchy rash)

Other side effects include

(frequency cannot be estimated from the available data)

- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood

sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.

- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.

- Skin and allergic reactions Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dosage. If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by calling Tel: 03-78835550, or visiting the website portal.bpfk.gov.my (Consumers → Reporting).

7. Storage and Disposal of Insuman Comb 50

Keep this medicine out of the

sight and reach of children.

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

Unopened vials

Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Comb 50 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials

Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

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

8. Product Description

What Insuman Comb 50 contains

-The active substance is insulin human. One ml of Insuman Comb 50 contains 100 IU (International Units) of the active substance insulin human. 50% of the insulin is dissolved in water; the other 50% is present as tiny crystals of insulin protamine.

-The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate,

glycerol, sodium hydroxide (see section 3 under “Important information about some of the ingredients of Insuman Comb 50”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 50 looks like and contents of the pack

After mixing, Insuman Comb 50 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 50 is supplied in vials containing 5 ml suspension (500 IU). Packs of 1 and 5 vials of 5 ml are available. Not all pack sizes may be marketed.

- MAL number:
MALxxxxxxxA

Manufacturer

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

Product Registration Holder

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HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.

Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA

(high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:

- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see *Using other medicines*).

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a

doctor, normally in a hospital.

HYPOGLYCAEMIA

(low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:

- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see *Using other medicines*).

Hypoglycaemia is also more likely to occur if:

- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

▪ **In your body**
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

▪ **In your brain**
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning

symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see *Using other medicines*).

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.

2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.

3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.

4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:

If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.
