ZANOSAR® 1 g

STREPTOZOCINE

Lyophilised powder for solution for injection

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

In this leaflet:

1. WHAT ZANOSAR IS AND WHAT IT IS USED FOR

Pharmacotherapeutic group

It is a cytotoxic medicine, which means that it inhibits the growth of certain cells. It is indicated especially in certain illnesses of the pancreas.

Therapeutic indications

This medicine may be used in combination with another medicine of the same class, 5-fluorouracile (5-FU). This combination has produced better results than when each treatment has been administered separately.

2. BEFORE YOU USE ZANOSAR

CONTRAINDICATIONS

◆ **DO NOT USE ZANOSAR**

- If you are allergic (hypersensitive) to the active substance (streptozocin) or any of the ingredients contained in ZANOSAR
- If you suffer from renal impairment (weak kidney function)
- In combination with the yellow fever vaccine

PRECAUTIONS FOR USE AND SPECIAL WARNINGS

◆ **TAKE SPECIAL CARE WITH ZANOSAR:**

- Due to the renal toxicity (in the kidneys) of this medicine, you should warn your doctor if you suffer from any kidney problems. In all cases, your kidney function will be monitored with blood and urine measurements before and during the treatment, and then every week for 4 weeks after the treatment.
- This medicine also presents with hepatic (liver) and haematological (blood) toxicity.
- When used in combination with another medicine of the same class, special monitoring measures should be taken.
- Hospitalisation during treatment is not essential, but it should be easy to monitor tolerance to the product (biological examinations, etc)
- **Monitoring during treatment.** This medicine should only be used under strict medical surveillance. A medical examination and blood analyses are necessary during treatment. Dose adjustment or treatment discontinuation may be necessary depending on the toxicity observed (toxic nature) of the treatment.

Using other medicines

You must not:

- Be vaccinated against yellow fever during the use of ZANOSAR
- Use other medicines that are toxic to the kidneys

Inform your doctor:

- If you are using or have recently used certain types of medicine for the treatment of epilepsy (phenytoin or phosphenytoin based medicines)

- If you need to be vaccinated against certain illnesses: measles, rubella, mumps, poliomyelitis, tuberculosis, chicken pox (live-attenuated vaccines)
- If are taking a medicine that lowers or suppresses your body's defenses (immunosuppressant)

The combination of this medicine with other medicines of the same class should be done cautiously since the toxicity of these medicines may add up.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Foods and beverages
Not applicable.

Interaction with phytotherapy products or alternative therapies
Not applicable.

◆ PREGNANCY AND BREASTFEEDING
Pregnancy
Administration of this medicine is not recommended in pregnant women.

Breastfeeding
It is not known whether the medicine is excreted in breast milk. By way of caution, you should stop breastfeeding during treatment.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
The effects on the ability to drive and use machines have not been studied. However, due to the side-effects, it is recommended that you do not drive or use certain tools or machinery during the days you receive the treatment.

List of excipients with a recognized effect
Not applicable.

3. HOW TO USE ZANOSAR ?

Dosage
The doctor will decide which dose to administer according to the surface area of your body and the treatment duration.
The treatment will be administered to you according to two different dosage schedules:
Either as a daily treatment for 5 consecutive days every 6 weeks
Or as a weekly treatment, namely once a week
If you have any other questions concerning the use of this medicine, please ask your doctor or pharmacist for more information.

Method of administration
This medicine must be prepared and administered only by a healthcare professional.
It will be administered to you intravenously (in a vein) directly or as a short (around 15 minutes) or prolonged infusion.
This treatment may also be combined with a medicine of the same class called 5-fluorouracile (5-FU).

4. POSSIBLE SIDE EFFECTS

Like all medicines, ZANOSAR can cause side effects, although not everybody gets them.

- Renal impairment (*weak kidney function*) that could be serious
- Significant nausea and vomiting that has sometimes required treatment discontinuation
- Diarrhoea
- Hepatic toxicity (*liver*)
- Bone marrow toxicity (*bone marrow*) and haematological toxicity (*blood*) have been rare, most often mild to moderate and reversible, and involving a mild decrease in haematocrit values (*percentage of red blood cell volume in relation to the total blood volume*) and anaemia (*decrease in haemoglobin level*). However, a few significant cases of leukopaenia (*abnormally low level of white blood cells in the blood*) and thrombocytopaenia (*abnormally low level of platelets in the blood – which have a significant role in blood coagulation–*) with fatal outcome have been reported

- Mild to moderate abnormalities in glucose (sugar) tolerance have been observed. Most often, they have been reversible
- Burning sensations from the site of injection up the arm have been reported in some patients
- Tissue necrosis (*destruction*) was observed when the product leaked out of the vein
- A temporary increase in some blood parameters was observed.
- Other: confusion, lethargy, depression and sometimes, fever in a limited number of patients.

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

5. HOW TO STORE ZANOSAR

Keep out of the reach and sight of children.
Do not use Zanosar after the expiry date stated on the box. The expiry date refers to the last day of the month.

Storage conditions
Store in a refrigerator (2°C – 8°C) and out of sunlight.
Storage time after reconstitution and dilution: Total storage time of reconstituted streptozocin should not exceed 48 hours between +2°C and +8°C or 24 hours at room temperature.
The product does not contain preservative and is for single-use only.
To avoid the risk of microbial contamination, it is recommended that the product be used immediately and within 12 hours following reconstitution of the solution.
Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ZANOSAR contains?
– The active substance is: Streptozocin 1g for one vial
– The other ingredients are: Anhydrous citric acid

What ZANOSAR looks like and contents of the pack?
This medicine is a lyophilised powder for injection preparation (box of 1 vial).

MA Holder
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Keocyt S.A.S – 29, rue chauvelot – 92240 Malakoff – France

Distributor
CSP – 76, avenue du midi – 63800 Cournon – France

MEDICAL INFORMATION AND PHARMACOVIGILANCE
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Manufacturer
Valdepharm – Parc Industriel d'Incarville – 27106 Val de Reuil – France

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The following information is intended for healthcare professionals only:

DOSAGE

This medicine should be administered intravenously or as a short (of around 15 minutes) or prolonged infusion. It is not active orally.

Two dosage schedules may be used:

– Daily schedule

The recommended dose for daily intravenous administration is 500 mg/m^2 of body surface area for five consecutive days every six weeks until maximum benefit or the onset of toxicity signs is observed. Dose escalation on this schedule is not recommended.

– Weekly schedule

The recommended dose for weekly intravenous administration is 1000 mg/m^2 of body surface area for the first two courses. For subsequent courses, doses may be escalated in patients in whom no therapeutic response was achieved and no signs of toxicity were observed during the previous course of treatment.

However, a single dose of 1500 mg/m^2 of body surface area should not be exceeded (renal toxicity).

With this schedule, the average response period is about seventeen days and the average time for maximum response is about thirty five days. Maximum response is understood to be the therapeutic response level which cannot be improved with dose escalation or increased treatment time.

The average total dose per course of treatment to achieve therapeutic response is around 2000 mg/m^2 of body surface area.

The average total dose to achieve maximum response is around 4000 mg/m^2 of body surface area.

The ideal duration of maintenance therapy has not yet been established for either treament schedule used.

For patients with functional tumours, regular monitoring of fasting insulin levels allows to determine the biochemical response to treatment.

For patients with either functional or non-functional tumours, response to treatment can be determined by measuring any significant reduction in the size of the tumour mass and adenopathies. For individuals with metastases of carcinoid tumours, response to treatment will be determined by measuring any significant reduction in the tumour volume of the metastases.

METHOD OF ADMINISTRATION

In case of extravasation, administration should be discontinued immediately.

WARNING:
It is extremely important to ensure intravenous administration. Any extravasation could risk leading to necrosis of the surrounding tissue. In case of extravasation, administration should be discontinued immediately.

INSTRUCTIONS FOR SAFE HANDLING

The preparation of cytotoxic agents for injection should be done by specialist and trained personnel with knowledge of the medicines used and in conditions guaranteeing the protection of the environment and especially the personnel handling the agents. It requires premises intended solely for preparation. Smoking, eating or drinking on these premises is forbidden. Personnel handling the agents should wear appropriate protective clothing including long-sleeved gowns, safety masks, safety cap, safety glasses, sterile single-use PVC gloves, work surface safety sheets, and waste-disposal containers and bags. Excreta and vomit should be handled with caution. Pregnant women should be warned and avoid handling cytotoxic agents. Any broken container should be handled with the same precautions and considered contaminated waste. Disposal of contaminated waste should be done by incineration in rigid, labelled waste-disposal bags.
These guidelines may be considered for the cancerology network (circular DGS/DH/98 N°98/188 dated 24 March 1998) in collaboration with any other appropriate structure and fulfilling the necessary conditions.

COMBINATION

This medicine may be used in combination with 5-fluoro-uracile (5-FU) according to the following schedule:
– Streptozocin 500 mg/m^2/day for 5 days
– 5-FU 400 mg/m^2/day for 5 days
Treatment should be renewed every six weeks.

The therapeutic dose of streptozocin should be adjusted according to patient tolerance. A dose reduction is recommended in patients with renal impairment. If creatinine clearance is around 10 to 50 ml/min, an equivalent dose of 75% of the theoretical dose should be administered, and if creatinine clearance is below 10 ml/min, the theoretical dose should be reduced by 50%. Dose reduction or treatment discontinuation should be considered in cases of hepatic impairment or signs of bone marrow toxicity (generally appearing in cases of streptozocin combination with a chemotherapeutic agent).

SPECIAL STORAGE PRECAUTIONS

Store in the refrigerator (2°C – 8°C) and protected from light.
Stability duration after reconstitution and dilution: the total storage time for reconstituted should not exceed 48 hours between 2°C and 8°C or 24 hours at room temperature.
The product does not contain any preservative and is not intended for multiple use.
In order to avoid any microbial contamination, it is recommended that the product be used immediately and within 12 hours from reconstitution of the solution.

LAST NOTICE REVISION

January 2008