ZANOSAR® 1g

Powder for concentrate for solution for infusion

STREPTOZOCIN

Read all of this leaflet carefully before you start taking this medicine, because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor, your pharmacist or your nurse.
- This medicine has been prescribed for you only. Do not pass it to others. It may harm them even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

1. What is Zanosar and what is it used for

This is a cytostatic medicine, which means that it prevents the growth of certain cells.
It is particularly indicated in adults for some tumours of the pancreas (neuroendocrine tumours). This medicine, which is injected intravenously, may be combined with 5-fluorouracil (5-FU).

2. What do you need to know before you use Zanosar

Zanosar must never be used:
- If you are allergic to the active substance (streptozocin) or any of the other ingredients of this medicine (listed in section 6),
- If you are suffering from severe renal impairment (failure of kidney function),
- In combination with certain vaccines (called live or live-attenuated vaccines),
- In case of breastfeeding.

Warnings and precautions
Because of the toxicity to the kidneys of this medicine you must inform your doctor if you suffer from kidney problems. Your renal function will always be monitored regularly by blood and urine measurements before, during and after treatment.

This medicine also has toxicity to the liver and to the blood. Liver function tests should be done on a regular basis to detect hepatotoxicity.

Zanosar can induce nausea and vomiting. Thus, your doctor can prescribe you some anti-vomiting medicinal products.

When it is combined with another medicine belonging to the same class, further appropriate investigations are performed.

You will be given your treatment under the supervision of a physician experienced in the administration of cytostatic medicinal products. He will decide in which setting your tolerance to the treatment will be monitored (laboratory tests, etc).

Men and women should use an effective method of contraception during and after treatment. Please see "Pregnancy, breastfeeding and fertility" below.

Monitoring during treatment
This medicine can only be used **under strict medical supervision**: a medical examination and blood tests are required during treatment. If you have any doubt, do not hesitate to ask your doctor or your pharmacist for advice.

Children and adolescents
The safety and efficacy of Zanosar have not been studied in children and adolescents under 18 years old.

Other medicines and Zanosar
Contraindicated associations
This medicine MUST NOT BE USED in the following situations:
- In combination or successive administration with other substances which are potentially toxic to the kidney (unless advised otherwise by your doctor).
- Combination with certain vaccines (called live or live-attenuated vaccines).

Associations requiring cautions
Alert your doctor:
- If you are taking a medicine which reduces or abolishes the body defences (immunosuppression),
- If you are taking oral anticoagulants (vitamin K antagonist).

Tell your doctor or pharmacist if you are taking, have recently taken or may take any other medicine.

Pregnancy, breastfeeding and fertility
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.

Contraception for men and women
You should use an effective method of contraception during treatment. A period of contraception post-treatment of 90 days for men, and 30 days for women should be applied.

Pregnancy
You should not use this medicine if you are pregnant or if you are planning to have a baby or if you do not use a method of contraception.

Breastfeeding
It has not been determined whether this medicine passes into breast milk. As a cautionary measure you should stop breastfeeding during treatment.

Fertility
If you are a man being treated with Zanosar, you are advised not to attempt to father a child for 90 days after treatment and to seek advice on conservation of sperm prior to treatment, because streptozocin may alter male fertility.

If you are a woman, you should continue your contraception for 30 days after treatment.

Driving and using machines
Zanosar may cause confusion, fatigue or depression, therefore you should not drive or use machines if you experience one of these effects.

3. How to use Zanosar

This medicine must **only** be prepared and administered by a healthcare professional.

Your doctor will determine the dose you should receive based on your body surface area and general state.

The treatment will be injected by infusion into one of your veins (intravenous use). The infusion will last from 30 minutes to 4 hours.

Two dosage schedules are generally used:
- Six-weekly regimen: 5 consecutive days every 6 weeks;
- Three-weekly regimen: 5 consecutive days during the first week, and then 1 infusion every 3rd week.

A dosage adjustment or discontinuation of treatment may be required if toxicity develops.

Zanosar can induce nausea and vomiting. Thus, your doctor can prescribe you some anti-vomiting medicinal products.

If you use more Zanosar than you should
Appropriate care measures will be provided to you.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everyone gets them.

Very common side effects (may affect more than 1 in 10 people)
Severe nausea and vomiting which have occasionally required discontinuation of the treatment. Cases of diarrhoea have also been reported.

Common side effects (may affect up to 1 in 10 people)
Renal impairment (failure of kidney function) which may be serious. Your doctor may prescribe blood and urine measurements for you before, during and then repeatedly after the end of the treatment.

Side effects of unknown frequency (frequency cannot be estimated from the available data)
- Haematological toxicity (blood toxicity) which usually involves a fall in haematocrit values (the percentage volume of red blood cells compared to the total blood volume), in white cells and in platelets. It may also increase the sensitivity to infections.
- Abnormalities of glucose tolerance, usually mild to moderate and usually reversible.
- Confusion, lethargy, depression.
- Nephrogenic diabetes insipidus (inability of the kidneys to concentrate urine).
- Hepatotoxicity (liver toxicity): increase in some liver enzymes, abnormally low level of albumin in the blood (hypoalbuminaemia).
- Injection site reactions: necrosis (destruction) of tissue when the substance passes outside the vein, burning sensations extending from the injection site to the arm.
- Fever.

Declaration of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:
Yellow card Scheme
Website: www.mhra.gov.uk/yellowcard
or search for MHRA Yellow Card in the Google Play or Apple App store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zanosar

Keep this medicine out of the sight and reach of children.

Do not use Zanosar after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.

Before opening: store the vial in a refrigerator (2°C to 8°C); keep the vial in the outer carton in order to protect from light.

After opening, reconstitution and dilution: The reconstituted solution should be immediately diluted. The chemical and physical in-use stability of the resulting solution has been demonstrated for 24 hours below 25°C.

The product does not contain a preservative and is for single use only.

From a microbiological point of view, unless the method of opening/ reconstitution/ dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use conditions are the responsibility of the user.

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.

6. Contents of the pack and other information

What Zanosar contains:
The active substance is:
Streptozocin ..... 1.000g (per a vial of powder)
The other ingredients are:
Anhydrous citric acid
Sodium hydroxide for pH adjustment

What Zanosar looks like and contents of the pack
This medicine is in the form of a sterile white to pale yellow powder for infusion preparation.
Box of 1 vial.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
KEOCYT
Immeuble Cap Sud
106, avenue Marx-Dormoy
92120 Montrouge
France

Manufacturer:
VALDEPHARM
Parc Industriel d'Incarville
27100 Val de Reuil
France

This medicine is authorised in the member states of the European Economic Area under the following names:
België/Belgique/Belgien: Streptozocine Keocyt 1g, poeder voor concentraat voor oplossing voor infusie

Danmark: Zanosar

Deutschland: Zanosar 1g, pulver für ein Konzentrat zur Herstellung einer Infusionslösung

Nederland: Zanosar 1g, poeder voor concentraat voor oplossing voor infusie

España: Zanosar 1g, polvo para concentrado para solución para perfusion

Norge: Zanosar 1g, Pulver til konsentrat til infusjonsvæske, oppløsning

France: Streptozocine Keocyt 1g, poudre pour solution à diluer pour perfusion

Italia: Streptozocina Keocyt

Suomi/Finland: Zanosar 1g, kuiva-aine välikonsentraatiksi infuusionestettä varten, liuos

Sverige: Zanosar 1g, pulver till koncentrat till infusionsvätska, lösning

United Kingdom: Zanosar 1g, powder for concentrate for solution for infusion

The last date on which this leaflet was revised is 08/2018.

Detailed information about this medicine is available on the MHRA (United-Kingdom) website.

The following information is intended for healthcare professionals only:

Posology:
The dose is based on the body surface area (m^2).

Two different dosage schedules can be used:
Six-weekly regimen – 500 mg/m^2/day, intravenously for 5 consecutive days every six weeks until maximum benefit or until treatment-limiting toxicity is observed.
Three-weekly regimen – 500 mg/m^2/day, intravenously for 5 consecutive days during cycle 1, followed by 1000 mg/m^2 every 3rd week during the subsequent cycles.

Other dosing regimens, with similar dose intensity, have been used in clinical studies with comparable efficacy and safety results.
The optimal duration of maintenance therapy with Zanosar has not been established.
For patients with functional tumours, serial monitoring of biological markers allows a determination of biochemical response to therapy. For patients with either functional or nonfunctional tumours, response to therapy can be determined by measurable reductions of tumour size on imaging.

A close monitoring of renal, hepatic and haematological functions must be performed before, during and after treatment, as well as blood glucose levels. Dose adjustment or discontinuation of the drug may be indicated, depending upon the degree of toxicity noted.

Antiemetic premedication is recommended to prevent nausea and vomiting.

Precautions to be taken before handling or administering the medicinal product
Caution in the handling and preparation of the powder and solution should be exercised, and the use of gloves is recommended. If the sterile powder of Zanosar or a solution prepared from Zanosar contacts the skin or mucosae, immediately wash the affected area with soap and water.
Procedures for proper handling and disposal of anticancer drugs should be considered.
The preparation of injectable solutions of cytotoxic agents should be done by specialist and trained personnel with knowledge of the medicines used and under conditions guaranteeing the protection of the environment and especially the personnel handling the agents. It requires premises intended solely for preparation. Smoking, eating and drinking in these premises is forbidden. Personnel handling the agents should have at their disposal a set of appropriate handling equipment particularly long sleeved gowns, safety masks, safety cap, safety glasses, sterile single-use PVC gloves, work surface safety sheets, 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 containers (labelled accordingly i.e. to indicate they contain such contaminated waste).

Overdose
There is no specific antidote for overdose with Zanosar and treatment of overdose should consist of supportive measures. Overdose should be avoided by carefully calculating the dose to be administered.

Method of administration
Zanosar should be administered intravenously by infusion. The duration of infusion should be between 30 minutes and 4 hours.
The administration of Zanosar requires hyperhydration.
This medicinal product is vesicant in nature and as such should be administered with caution through a free-flowing line.
In case of extravasation, administration should be stopped immediately. Healthcare professionals should take appropriate protection measures.
The initial aim is to minimize the volume of extravasated product into the surrounding tissues and to aspirate as much as possible product from the canula with a syringe. Cold packs should be applied and appropriate medical monitoring should be performed.

Instructions for reconstitution
Zanosar must be reconstituted by a healthcare professional.
Dose preparation takes into account the patient body surface area (see section posology above).
Each 20 mL vial of Zanosar must be reconstituted with 9.5 mL of a sodium chloride 9 mg/ml (0.9%) solution for injection. Dissolution of the lyophilised powder is completed in less than 2 minutes.
The resulting solution is pale-gold.
The pH value of the reconstituted product is 4.
After reconstitution, each mL solution contains 100 mg streptozocin per mL.
The correct amount of the reconstituted solution (see section 4.2 of the SmPC for the calculation of the dose based on the body surface area) should then be diluted in 500 mL of the same solution that was used for reconstitution.
In case of co-administration of Zanosar and 5-FU, it is recommended to use Y-set system.