SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zanosar 1 g, powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Zanosar vial contains 1 g of the active ingredient streptozocin.
The concentration of the reconstituted solution before dilution is 100 mg/mL.

Excipient(s) with known effect: Each vial contains 30.1 mg sodium.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

Zanosar is a freeze-dried preparation available as a sterile, white to pale yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zanosar is indicated for the systemic treatment of adult patients with inoperable, advanced or metastatic, progressive and/or symptomatic, well-differentiated, G1 or G2 neuroendocrine tumours of pancreatic origin, in combination with 5-Fluorouracil (see section 5.1).

4.2 Posology and method of administration

Zanosar should only be administered under the supervision of a physician experienced in the use of anti-cancer chemotherapeutic agents.

The patient should have access to a facility with a laboratory and supportive resources sufficient to monitor drug tolerance and to protect and maintain a patient compromised by drug toxicity.

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 6 weeks until maximum benefit is obtained or until treatment-limiting toxicity is observed. Dose escalation on this schedule is not recommended.

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. **However, a single dose of 1500 mg/m^2 of body surface area should**

not be exceeded (renal toxicity).

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.

Renal, hepatic and hematological function must be closely monitored before, during and after treatment, as well as blood glucose levels (see section 4.4). 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.

Method of administration

Zanosar should be administered intravenously by infusion (See section 6.6). The duration of infusion should be between 30 minutes and 4 hours.

The administration of Zanosar requires hyperhydration (see section 4.4).

This medicinal product is vesicant in nature and as such should be administered with caution through a free-flowing line.

In the event of extravasation, the administration should be discontinued immediately.

Special populations:

Patients with renal impairment:

Based on clinical practice, the dose of Zanosar should be adapted according to renal function: dose reduction or treatment discontinuation is mandatory in the presence of significant renal toxicity.

Estimated Glomerular Filtration Rate (GFR)	> 60 ml/min	≤ 60 ml/min and > 45 ml/min	≤ 45 ml/min and > 30 ml/min	≤ 30 ml/min
Dose of Zanosar	Full dose	Dose reduced by 50%	Evaluation of the benefit/risk ratio	Contra indicated (see sections 4.3 and 4.4)

If GFR is comprised between 30 and 45 ml/min, the benefit/risk ratio should be thoroughly evaluated in a multidisciplinary approach, which includes soliciting a nephrologist's opinion and balancing the potential benefit against the known risk of serious renal damage.

Hepatic impairment:

Dose reduction should be considered in cases of hepatic impairment (see section 4.4).

Elderly population:

The safety and efficacy of Zanosar in patients aged ≥ 65 years have not been established .

Regimen selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapies.

Paediatric population:

The safety and efficacy of Zanosar in patients below 18 years have not been established

For precautions to be taken before handling or administering the medicinal product, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Renal failure (GFR < 30 ml/min) (see section 4.4)
- Live and live-attenuated vaccines
- Breastfeeding

4.4 Special warnings and precautions for use

Renal Toxicity :
Many patients treated with Zanosar have experienced some degree of renal toxicity, as evidenced by an increase in plasma creatinine and proteinuria. The mechanisms of renal toxicity are still unclear but experimental and clinical data suggest tubular toxicity, such as tubular acidosis, low molecular weight proteinuria, hypokalemia and hypocalcaemia.
Such toxicity is dose-related and cumulative in most cases and may be severe or fatal. However, it can also appear after the first administration.

Renal function must be monitored immediately before and two weeks after each course of therapy. Routine surveillance consists of the measurement of plasma creatinine with the evaluation of glomerular filtration rate (GFR) by the Modification of Diet in Renal Diseases (MDRD) formula. Before the initiation of treatment (i.e. before the first cycle of therapy) and two to four weeks after the end of the last cycle of therapy, proteinuria and serum electrolytes should also be measured, in addition to plasma creatinine.

Reduction of the dose of Zanosar or discontinuation of treatment is mandatory in the presence of significant renal toxicity (see section 4.2).
Adequate hydration with at least one litre of sodium chloride 0.9% before the administration of Zanosar may help reduce the risk of toxicity to the renal tubular epithelium by decreasing renal and urinary concentration of the drug and its metabolites.
Use of Zanosar in patients with preexisting renal disease requires a judgment by the physician of the potential benefit of treatment as opposed to the known risk of serious renal damage.
This drug should not be used concomitantly with other potential nephrotoxic drugs.

Hepatotoxicity:
Liver function tests should be done on a regular basis, to detect hepatic toxicity. Reduction of the dose or discontinuation should be considered in case of hepatic toxicity.

Haematologic toxicity:
Complete blood counts should be done on a regular basis, to detect haematologic toxicity. Reduction of the dose or discontinuation should be considered in case of haematologic toxicity (usually due to the association of Zanosar with another chemotherapy).
Haematological toxicity has been rare, most often involving mild decreases in haematocrit values. However, fatal haematological toxicity with substantial reductions in leukocyte and platelet count has been observed.
Rare cases of myelodysplastic syndromes or acute myeloid leukemia have been reported in patients previously treated by a streptozocin-based chemotherapy, who received subsequent peptide receptor radionuclide therapy

Immunosuppressive effects, increased sensitivity to infections:
The administration of live or live-attenuated vaccines in patients with chemotherapy-related immunodeficiency, including streptozocin, may provoke severe or life-threatening infections. Dead or inactivated vaccines can be administered; however, they can induce lower response in this population (see sections 4.3 and 4.5).

Nausea and vomiting:
Streptozocin is associated with a high emetic potential which may be treatment-limiting. Antiemetic premedication is recommended to prevent nausea and vomiting.

Injection-Site reactions: □
Zanosar sterile powder is irritating to tissues. Extravasation may cause severe tissue lesions and necrosis.
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 cannula with a syringe. Cold packs should be applied and appropriate medical monitoring should be performed.

Sodium:
This medicinal product contains 30,1mg sodium per vial equivalent to 1,5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Live and live-attenuated vaccines: Concomitant use may induce fatal generalized vaccinal disease and is contraindicated (see section 4.3).

Immunosuppressive drugs: increased immunosuppression with a risk of lymphoproliferative disorders.

Vitamin K antagonists: The important intra-variability of the coagulation status and of the increased thrombotic and haemorrhagic risks during tumour diseases, and the potential interaction between oral anticoagulants and anticancer chemotherapy, require increased frequency of INR (International Normalised Ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.

Nephrotoxic drugs: Zanosar should not be used in association with nephrotoxic drugs.

4.6 Fertility, pregnancy and lactation

Contraception:

Zanosar is not recommended in women of childbearing potential not using contraception. An effective method of contraception should be used during treatment. A period of contraception post-treatment of 90 days for men, and 30 days for women should be applied.

Pregnancy:

There are no data from the use of Zanosar in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3).

Zanosar is not recommended during pregnancy.

Zanosar should be used in pregnancy only if the potential benefit to the mother outweighs the potential risks to the fetus.

Lactation:

It is unknown whether streptozocin and/or its metabolites are excreted in human milk. A risk to the newborns / infants cannot be excluded. Therefore, breast-feeding should be discontinued during treatment with Zanosar.

Fertility:

There are no data on fertility in humans. In non-clinical studies, streptozocin adversely affected fertility when administered to male and female rats (see section 5.3). Therefore, men being treated with streptozocin 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.

4.7 Effects on ability to drive and use machines

Streptozocin may cause confusion, lethargy or depression.

Patients should be advised not to drive or use machines if they experience any adverse reaction that may affect their ability to perform these tasks.

4.8 Undesirable effects

The most common adverse reactions reported with Zanosar are gastrointestinal and renal disorders.
The former are not life threatening but can be disturbing for the patient and may result in treatment discontinuation if very severe; the latter are indolent but potentially serious.
The frequency and intensity of nausea and vomiting has decreased over time, due to the utilization of efficacious antiemetic drugs. Renal toxicity can be avoided or reduced with careful assessment of renal function before and during treatment, patient hydration during streptozocin administration, and dose adjustment in case of renal function impairment.
Streptozocin has the potential to cause hyperglycaemia due to its mechanism of action; however, glucose intolerance or diabetes have been rarely reported in clinical practice.
Myelotoxicity is usually mild and transient. Hepatic toxicity has been described, but not reported as a major issue during treatment.

Tabulated list of adverse reactions (from published data and post-marketing experience):
Adverse reactions are listed below by MedDRA system organ class and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (cannot be estimated from the available data).

MedDRA system organ class	Very common adverse reactions	Common adverse reactions	Frequency not known
Blood and lymphatic system disorders			Decreased haematocrit, leukocytes and platelet counts
Metabolism and nutrition disorders			glucose intolerance
Nervous system disorders			Confusion, lethargy, depression
Gastrointestinal disorders	Severe nausea and vomiting, Diarrhoea		Nephrogenic diabetes insipidus
Hepatobiliary disorders			Elevated liver enzymes (SGOT and LDH) Hepatotoxicity Hypoalbuminemia
Renal and urinary disorders		Renal toxicity – proteinuria, proximal tubular injury, phosphaturia, acute renal failure Urinary disorders	
General disorders and administration site conditions			Fever, Injection site reactions

Gastrointestinal disorders:
Patients treated with Zanosar have experienced nausea and vomiting. In the earliest studies, up to 80-90% of patients reported nausea and vomiting, while in the most recent ones, this percentage ranges from 23 to 37%. In the earliest studies, severe nausea and vomiting was reported in 20 to 41% of patients. In a randomized study published in 2014, grade 3-4 nausea and vomiting was reported in 4.6% of patients. Severe nausea and vomiting occasionally required discontinuation of drug therapy. Some patients experienced diarrhoea.

Renal and urinary disorders:
Literature data suggest that renal and urinary disorders are frequent. Renal toxicity is dose-related and cumulative in most cases and may be severe or fatal.
However, an accurate incidence cannot be provided in the absence of recent prospective studies, using comprehensive toxicity reporting. In prospective studies

published after 2000, no grade 3 to 5 toxicity was reported (See section 4.4).

Hepatobiliary disorders:

Serum aminotransferase elevations can occur in up to two-thirds of patients treated with streptozocin, but the abnormalities are generally mild, transient and not associated with symptoms or jaundice. Rarely, severe cases have been reported (see section 4.4).

Blood and lymphatic system disorders:
Acute haematological toxicity is rare, consisting most often of mild decreases in haematocrit values, leukocytes and platelets counts. However, fatal haematological toxicity with substantial reductions in leukocyte and platelet count has been observed. Haematological toxicity may increase the sensitivity to infections.
Rare cases of late haematological toxicity (myelodysplatic syndrome or acute myeloid leukemia) have been reported in patients previously treated by a streptozocin-based chemotherapy, who received subsequent peptide receptor radionuclide therapy.

Metabolism and nutrition disorders (see section 5.1):
Mild to moderate glucose intolerance has been noted in patients treated with Zanosar. These have generally been reversible.
Due to the mechanism of action of streptozocin, diabetes cannot be excluded.

General disorders and administration site conditions:
Severe tissue necrosis has been described following extravasation. Burning sensation, extending from injection site to the arm has been reported in some patients following bolus administration.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic alkylating agent - Nitrosoureas

ATC code: L01AD04

Mechanism of action:

The antineoplastic activity of streptozocin was assessed *in vitro*, and *in vivo*, using mice bearing different tumor types.

Streptozocin undergoes spontaneous decomposition to produce reactive methylcarbonium ions that alkylate DNA and cause interstrand cross-links. Severe DNA damage by streptozocin results in cell death by apoptosis or necrosis. Furthermore, the DNA strand breaks resulting from the alkylating action of streptozocin can lead to chromosomal rearrangements. In addition, cytogenetic damage by streptozocin can be manifested as chromosomal aberrations, sister chromatid exchanges or micronuclei.

In comparison with other nitrosoureas, the alkylating activity of Zanosar is weak: the methylnitrosourea metabolite has 3 to 4 times the alkylating activity of the parent compound. The presence of the glucose moiety reduces the alkylating action, but also reduces the bone marrow toxicity.

Clinical efficacy:

In clinical studies, Zanosar in combination with 5-fluorouracil demonstrated a benefit in the treatment of pancreatic neuroendocrine tumours, with response rates of 20 to 40%.

Randomized clinical trials

Three randomized clinical studies evaluated the efficacy and safety of streptozocin in pancreatic neuroendocrine tumours.

The high responses obtained in the first two trials were based on assessment of biochemical markers and clinical hepatomegaly. These high response rates have not been achieved in later studies, due more stringent efficacy criteria.

Moertel 1980: streptozocin alone vs. streptozocin + 5-FU

- 84 patients included
- Response rates (RR) 36% with streptozocin alone vs. 63% with streptozocin + 5-FU

Moertel 1992: streptozocin + doxorubicin vs. streptozocin + 5-FU vs. chlorozotocin

- 105 patients included.
- RR: 69% with streptozocin + doxorubicin vs. 45% with streptozocin + 5-FU
- Median survival: 2.2 and 1.4 years respectively

Meyer 2014: streptozocin + capecitabine vs. streptozocin + capecitabine + cisplatin

- 86 patients included (pancreatic and non- pancreatic NETs)

- RR: 12% streptozocin + capecitabine vs. 16% with streptozocin + capecitabine + cisplatin; in patients with pancreatic NETs (48%), response rate was 17% irrespective of treatment

- Disease control rate (DCR): 80% and 74% respectively. In patients with pancreatic NETs, DCR was 86% irrespective of treatment.

- Median progression free survival (PFS) and overall survival (OS) with the streptozocin + capecitabine regimen were 10.2 and 26.7 months respectively.

Non-randomized prospective studies

Eriksson 1990: streptozocin + doxorubicin vs. streptozocin + 5-FU

- RR: 36% (9/25) with streptozocin + doxorubicin and 58% (11/19) with streptozocin + 5-FU

- Duration of response: 22 months and 36 months respectively

Prospective non-comparative studies

Turner 2010 : Streptozocin + 5-FU

- Response rate 38.3% (18/47) (Turner *et al*, 2010),

5.2 Pharmacokinetic properties

After i.v. administration of radiolabeled streptozocin, the unchanged drug was cleared from the plasma within a few minutes (initial half-life: 5 minutes and terminal half-life: 35 minutes). The metabolites had a much longer half-life (>24H). These metabolites entered the central nervous system whereas there was no parent drug in the cerebrospinal fluid. Around 30% of the dose was excreted in urine as nitrosourea containing metabolites during the first 24 hours after dose. Parent drug accounted for 10-20% of the renal excretion. Less than 1% of the radiolabeled dose was recovered in faeces.

In vitro data did not indicate involvement of microsomal CYP enzymes in the degradation of streptozocin. Streptozocin was not found to inhibit CYP450 enzymes in vitro.

5.3 Preclinical safety data

Conventional studies with streptozocin, including short term toxicology studies, genotoxicity and reproductive toxicity studies were conducted in mice, rats, rabbits, dogs and monkeys.

Repeated dose studies in dogs and monkeys given intravenous injections of streptozocin show systemic toxicity at clinically relevant doses.

No formal carcinogenicity studies were conducted with streptozocin. In line with its pharmacological action, streptozocin is genotoxic (see section 5.1). Consequently, streptozocin may pose a carcinogenic hazard following topical exposure if not properly handled (see section 6.6).

At clinically relevant doses, streptozocin adversely affected fertility in male and female rats and induced embryo-foetal toxicity, in rats and rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous.

Sodium hydroxide for pH adjustment

6.2 Incompatibilities

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

6.3 Shelf life

Before opening: 36 months
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 in polyethylene Ecoflac® type bag containing a sodium chloride 9 mg/ml (0.9%) solution for injection.
The product does not contain any 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.

6.4 Special precautions for storage

Store the vial in a refrigerator (2°C to 8°C);
The vial can be stored below 25 ° C during 4 days before use.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder in a 20 mL type I glass vial with a bromobutyl rubber stopper and sealed with an aluminium / plastic flip-off cap.

1 vial.

6.6 Special precautions for disposal

General precautions

Streptozocin is a cytotoxic agent. Therefore, caution should be used during handling and preparation of Zanosar. Use of gloves and other protective clothing to prevent skin contact is recommended.

Aseptic technique must be strictly observed throughout the handling of Zanosar, since it contains no preservative.

Instructions for reconstitution

Zanosar must be reconstituted by a healthcare professional.

Dose preparation takes into account the patient body surface area (see section 4.2).

Each 20 mL vial of Zanosar must be reconstituted with 9.5 mL of 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 around 4.

After reconstitution, each mL solution contains 100 mg streptozocin per mL.

The correct amount of the reconstituted solution (see section 4.2 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 an Y-set system.

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).

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

7 MARKETING AUTHORISATION HOLDER

ESTEVE PHARMACEUTICALS S.A.S.

Immeuble Cap Sud

106 avenue Marx Dormoy

92120 Montrouge

FRANCE

8 MARKETING AUTHORISATION NUMBER(S)

PL 40308/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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