PRODUCT MONOGRAPH

PrZANOSAR® STERILE POWDER

(streptozocin for injection)

ANTINEOPLASTIC AGENT

Paladin Labs Inc
6111 Royalmount Ave
Montreal, Quebec H4P 2T4

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CAUTION: ZANOSAR (STREPTOZOCIN) SHOULD BE ADMINISTERED UNDER THE SUPERVISION OF A PHYSICIAN EXPERIENCED IN THE USE OF CANCER CHEMOTHERAPEUTIC AGENTS (SEE WARNINGS AND PRECAUTIONS). RENAL, HEPATIC AND BONE MARROW/HEMATOLOGIC EVALUATIONS SHOULD BE DONE AT REGULAR INTERVALS. RENAL TOXICITY IS DOSE RELATED AND CUMULATIVE AND MAY BE FATAL.

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

ACTION AND CLINICAL PHARMACOLOGY

ZANOSAR (streptozocin) inhibits DNA synthesis in bacterial and mammalian cells. In bacterial cells, a specific interaction with cytosine moieties leads to degradation of DNA. The biochemical mechanism leading to mammalian cell death has not been definitively established; levels required to kill cells are considerably lower than those required to inhibit DNA synthesis or to inhibit several of the enzymes involved in DNA synthesis.

ZANOSAR inhibits the progression of cells into mitosis but the agent does not appear to be specifically lethal to cells in a single phase of the cell cycle.

ZANOSAR is active in the L1210 leukemic mouse over a fairly wide range of parenteral dosage schedules. In many experimental animal species, ZANOSAR induces a diabetes that resembles human hyperglycemic non-ketotic diabetes mellitus. This phenomenon, which has been extensively studied, is consequent upon histopathologic alteration of pancreatic islet *beta* cells.

The metabolism of ZANOSAR has not been fully studied. When given intravenously to mice or dogs, it disappears from the blood very rapidly. In all species tested, it concentrates in the liver and kidney. Less than 10% of the drug (or metabolites containing an N-nitrosourea group) is excreted by the kidney. Metabolic products have not been identified.

INDICATIONS AND CLINICAL USE

ZANOSAR (streptozocin) is indicated for the treatment of metastatic islet cell carcinoma of the pancreas. Responses have been obtained with both functional and non-functional carcinomas. Because of its inherent renal toxicity, therapy with this drug should be limited to patients with symptomatic or progressive metastatic disease.

CONTRAINDICATIONS

ZANOSAR (streptozocin) is contraindicated in patients with known hypersensitivity to the drug.

Pre-existing renal disease is a strong contraindication to the use of ZANOSAR. Use of the drug in such a patient must be judged by the physician in terms of the potential benefit as opposed to the known risk.

WARNINGS

ZANOSAR (streptozocin) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Renal Function:
Many patients treated with ZANOSAR have experienced renal toxicity as evidenced by azotemia, anuria, hypophosphatemia, glycosuria and renal tubular acidosis. Such toxicity is dose-related and cumulative and may be severe or fatal. Renal function must be monitored before and after each course of therapy. Serial urinalysis, blood urea nitrogen, plasma creatinine, serum electrolytes and creatinine clearance should be obtained prior to, at least weekly during, and 4 weeks after drug administration. Serial urinalysis is particularly important for the early detection of proteinuria and should be quantitated with 24 hour collection when proteinuria is detected.

Mild proteinuria and hypophosphatemia are the first signs of renal toxicity and may herald further deterioration of renal function. Reduction of the dose of ZANOSAR or discontinuation of treatment is suggested in the presence of significant renal toxicity.

This drug should not be used in combination with or concomitantly with other potential nephrotoxins.

During therapy, a patient need not be hospitalized but should have access to a facility with laboratory and supportive resources sufficient to monitor drug tolerance and to protect and maintain a patient compromised by drug toxicity.

Other toxicities are nausea and vomiting, which may be severe and at times treatment-limiting. In addition, liver dysfunction, diarrhea, and bone marrow / hematological changes have been observed in some patients.

Effects at Site of Injection
Care should be taken to avoid extravasation of the drug, since under such conditions severe local tissue necrosis will occur.

Immunosuppressant Effects/Increased Susceptibility to Infections
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including streptozocin may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving streptozocin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Mutagenesis, Carcinogenesis, Impairment of Fertility
Streptozocin is mutagenic in bacteria, plants and mammalian cells. When administered parenterally, it has been shown to induce renal tumors in rats and to induce liver tumors and other tumors in hamsters. Stomach and pancreatic tumors were observed in rats treated orally with streptozocin. Streptozocin has also been shown to be carcinogenic in mice.

Streptozocin adversely affected fertility when administered to male and female rats.

When exposed dermally, some rats developed benign tumors at the site of application of streptozocin. Consequently, streptozocin may pose a carcinogenic hazard following topical exposure if not properly handled. If ZANOSAR powder or solution contacts the skin or mucosae, immediately wash the affected area with soap and water. (See Special Instructions under PHARMACEUTICAL INFORMATION).

PRECAUTIONS

Patient Follow-up:
Patients who are treated with ZANOSAR (streptozocin) must be monitored closely, particularly for evidence of renal, hepatic, and bone marrow/hematopoietic toxicity. Serial urinalysis, blood urea nitrogen, and plasma creatinine levels, and creatinine clearance should be done prior to and at least once weekly during and for 4 weeks after drug administration. (See WARNINGS - Renal toxicity).

Similarly, complete blood counts and liver function studies should be done weekly. Reduction of the dose or discontinuation of ZANOSAR therapy is suggested in response to the appearance of significant renal, hepatic, or bone marrow/hematopoietic abnormalities, but must be weighed against the possible benefit of continued therapy of clinically progressive disease.

Storage Limitations:
After reconstitution, the solution may be stored in a refrigerator for 48 hours. However, this formulation contains no preservatives, and is not intended as a multiple-dose vial. (See Storage under DOSAGE AND ADMINISTRATION).

Interaction with Other Medications:
When streptozocin is used in combination with antineoplastic drugs with similar cytotoxic effects, additive toxicity is likely to occur.

Streptozocin has been reported to prolong the elimination half-life of doxorubicin leading to increased severe bone marrow suppression. In case of concomitant administration of the two drugs, a reduction of doxorubicin dosage should be considered.

The administration of amphotericin B with antineoplastic drugs, including streptozocin, may increase the risk of nephrotoxicity, hypotension and bronchospasm. If it is necessary to give this combination of agents, a close monitoring of blood pressure as well as renal and pulmonary function is advisable.

The concurrent use of streptozocin and phenytoin has been reported in one case to result in reduced streptozocin cytotoxicity.

Concomitant use of steroids with streptozocin may result in severe hyperglycemia.

Usage in Pregnancy:
Safe use of ZANOSAR during pregnancy has not been established. ZANOSAR is mutagenic in bacteria and plants. By analogy with other nitrosoureas, it would be expected to exhibit teratogenic effects in animals.

When administered to pregnant monkeys, it appears promptly in the fetal circulation. It has been shown to induce renal tumors in rats, and liver and other tumors in hamsters. The physician must judge the possible

benefit to his patient against these known toxic effects when considering the advisability of therapy with ZANOSAR in males or females who may contemplate the initiation of pregnancy, or in pregnant females.

Reproduction studies revealed that streptozocin is teratogenic in the rat and has abortifacient effects in rabbits. There are no studies in pregnant women.

ZANOSAR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of child-bearing potential who are to undergo streptozocin therapy should be informed of the potential hazard to the fetus and should be advised to avoid becoming pregnant during treatment.

Nursing Mothers:
It is not known whether streptozocin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, nursing should be discontinued in patients receiving ZANOSAR.

Usage in Children:
No data on treatment of children are available.

Effects on patients ability to operate a vehicle or Machinery:
On the basis of reported adverse reactions (i.e. confusion, lethargy), streptozocin may potentially increase the risk of injury while driving or operating machinery.

ADVERSE REACTIONS

Renal and Urinary Disorders (See WARNINGS)
Renal toxicity is the most serious and dose-limiting adverse effect of ZANOSAR (streptozocin) treatment, occurring in approximately 25-75% of treated patients. Streptozocin-induced nephrotoxicity is cumulative and may be severe or fatal. Increase of BUN, anuria, proteinuria, hypophosphatemia, hyperchloremia, and proximal renal tubular acidosis which may be associated with a Falconi-like syndrome evidenced by glycosuria, acetonuria and aminoaciduria are manifestations of glomerular and tubular function abnormalities. Hypokalemia and hypocalcemia have also occurred. Hypophosphatemia and mild proteinuria appear to be the earliest signs of nephrotoxicity, whereas increase of BUN and serum creatinine concentrations usually develop later following continued treatment with the drug.

Although mild renal adverse effects may be reversible following discontinuation of streptozocin, nephrotoxicity may be irreversible and fatalities associated with chronic renal failure may occur if therapy with the drug is continued after nephrotoxicity is observed.

Cases of nephrogenic diabetes insipidus following ZANOSAR therapy have been reported. One had spontaneous recovery and the second responded to indomethacin.

Gastrointestinal Disorders:
Most patients treated with ZANOSAR have experienced severe nausea and vomiting, occasionally requiring discontinuation of drug therapy. Nausea and vomiting usually begin within 1-4 hours following administration of streptozocin and may persist for 24 hours or longer. Incidence and severity of nausea and vomiting may be reduced with 5-day continuous i.v. infusion. Conventional antiemetics (e.g., phenothiazines) are usually only minimally effective in preventing or reducing streptozocin-induced nausea and vomiting. Some patients experienced diarrhea. Increases in serum bilirubin concentration and hypoalbuminemia have also been reported.

Hepatobiliary Disorders:
Severe and fatal hepatic effects have occurred rarely (see Investigations below).

Metabolism and Nutrition Disorders:
Mild to moderate abnormalities of glucose tolerance have been noted in some patients but these have generally been reversible. Insulin shock with severe hypoglycemia has occurred rarely during streptozocin therapy in patients with insulinomas, usually within 24 hours after administration of the drug.

Blood and Lymphatic System Disorders:
Bone Marrow/Hematological toxicity has been rare, most often involving mild decreases in hematocrit values. However, fatal hematological toxicity, resulting from leukopenia (leading to sepsis) and from thrombocytopenia has been observed. Mild to moderate myelosuppression, which may be manifested as leukopenia/neutropenia, thrombocytopenia and anemia (decreased hematocrit and hemoglobin concentrations) occurs in 10-20% of patients receiving the drug. Myelosuppression may be cumulative and may be more severe in patients previously treated with other antineoplastic agents or radiation therapy. Leukocyte and platelets nadirs generally occur 1-2 weeks following treatment with the drug. Asymptomatic eosinophilia, which disappeared following discontinuance of streptozocin, has also been reported.

Investigations
Transient increases in serum concentrations of AST, ALT, LDH and/or alkaline phosphatase have been reported. Increases in serum bilirubin concentration and hypoalbuminemia have also been reported.

General Disorders and Administration:
Severe necrosis has been reported following extravasation of the drug. A burning sensation, extending from the site of injection up the arm, has been reported in some patients especially following i.v. push administration. Pyrexia has occurred rarely.

Nervous System Disorders/Psychiatric Disorders
Confusion, lethargy and depression, have been reported in a limited number of patients receiving continuous i.v. infusion for 5 days. Adverse CNS effects have not been associated with other regimens.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No specific antidote for ZANOSAR (Streptozocin) is known, thus every possible measure should be taken to avoid an overdose; this includes full awareness of the potential danger of an overdose, careful calculation of the dose to be administered and availability of adequate diagnostic and treatment facilities.

DOSAGE AND ADMINISTRATION

ZANOSAR should be administered intravenously. It is not active orally. Although it has been administered intra-arterially, this is not recommended pending further evaluation of the possibility that adverse renal effects may be evoked more readily by this route of administration.

Dosage Schedules:
Two different dosage schedules have been employed successfully with ZANOSAR.

Daily Schedule:
The recommended dose for daily intravenous administration is 500 mg/m^2 of body surface area for 5 consecutive days every 6 weeks until maximum benefit or until treatment-limiting toxicity is observed. Dose escalation on this schedule is not recommended.

Weekly Schedule
The recommended initial dose for weekly intravenous administration in 1000 mg/m^2 of body surface area at weekly intervals for the first two courses (weeks). In subsequent courses, drug doses may be escalated in patients who have not achieved a therapeutic response and who have not experienced significant toxicity with the previous course of treatment. However, A SINGLE DOSE OF 1500 mg/m^2 BODY SURFACE AREA SHOULD NOT BE EXCEEDED as a greater dose may cause azotemia.

When administered on this schedule, the median time to onset of response is about 17 days and the median time to maximum response is about 35 days. The median total dose to onset of response is about 2000 mg/m^2 body surface area and the median total dose to maximum response is about 4000 mg/m^2 body surface area.

When ZANOSAR is used in combination with other chemotherapeutic agents, reduction of dosage is often necessary.

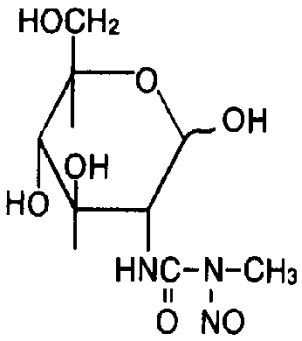
The ideal duration of maintenance therapy with ZANOSAR has not yet been clearly established for either of the above schedules.

For patients with functional tumors, serial monitoring of fasting insulin levels allows a determination of biochemical response to therapy. For patients with either functional or non-functional tumors, response to therapy can be determined by measurable reductions of tumor size (reduction of organomegaly, masses, or lymph nodes).

PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Streptozocin sterile powder
Chemical Name: (2-deoxy-2-(3-methyl-3-nitrosoureido)α (and β)-D-glucopyranose)
Structural Formula:



Molecular weight: 265.2
Molecular formula: $C_8H_{15}N_3O_7$

Description:
Streptozocin is a synthetic antineoplastic agent that is chemically related to other nitrosoureas used in cancer chemotherapy. Streptozocin is an ivory-colored crystalline powder. It is very soluble in water or physiological saline and is soluble in alcohol. Streptozocin melts with violent decomposition at about 115°C.

Composition:
Each vial contains streptozocin 1g, and 220 mg citric acid anhydrous. When necessary the pH was adjusted with sodium hydroxide and/or hydrochloric acid.

Stability and Storage Recommendations:
Unopened vials of ZANOSAR should be stored at refrigeration temperatures (2-8°C) and protected from light (preferably stored in carton).

The total storage time for streptozocin after it has been placed in solution should not exceed 48°hours at refrigeration temperatures (2-8°C) or 24 hours at room temperature (below 25°C). However, since this product contains no preservatives and is not intended as a multiple-dose vial and in order to avoid the risk of microbial contamination, it is recommended that the solution be used as soon as possible and within 12 hours from reconstitution.

Further dilution of the reconstituted solution with 500 mL of Sodium Chloride Injection USP does not alter the solution stability.

Incompatibilities:

Streptozocin has been reported to be incompatible with allopurinol in sodium chloride 0.9% solution, resulting in drug precipitation. Aztreonam or piperacillin/tazobactam diluted in 5% dextrose cause solution colour changes and are to be considered incompatible.

Reconstituted Solutions:
Reconstitute ZANOSAR with 9.5 mL of Dextrose Injection USP, Sterile Water for Injection USP, or Sodium Chloride Injection USP. The resulting pale-gold solution will contain 100 mg of streptozocin and 22 mg of citric acid per mL. Where more dilute infusion solutions are desirable, further dilution in the above vehicles is recommended. When reconstituted as directed, the pH of the solution will be between 3.5 and 4.5.

Special Instructions:

Handling:
The following precautionary measures are recommended in proceeding with preparation and handling of cytotoxic agents such as ZANOSAR (streptozocin).

1. Pregnant staff should be excluded from working with this drug;
2. Personnel should be trained in good technique for reconstitution and handling;
3. The procedure should be carried out in a vertical laminar flow hood (biological Safety Cabinet - Class II). The work surface should be protected by disposable, plastic-backed, absorbent paper.
4. Personnel should wear: PVC gloves, safety glasses, disposable gowns and masks.
5. All items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk waste-disposal bags for high-temperature incineration.
   Streptozocin waste should be deactivated by reaction with hydrobromic acid in glacial acetic acid or by oxidation with a solution of potassium permanganate in sulphuric acid.

AVAILABILITY OF DOSAGE FORMS

ZANOSAR (streptozocin) is supplied as 1 g vials and contains an off white to pale yellow colored freeze-dried cake.

PHARMACOLOGY

In mice, the serum half-life of streptozocin after an intravenous injection (200 mg/kg) was approximately 5 minutes with no drug measurable by 2 hours. Streptozocin was detectable in the acid-soluble fraction of liver for 20 hr, and it was found that nicotinamide pre-treatment did not significantly alter the drug uptake by this organ.

When injected intravenously in dogs, streptozocin disappears from the bloodstream at a very rapid rate. From intravenous infusion studies in dogs, the degradation rate has been estimated to be 5 mg/min in anesthetized animals.

When injected intramuscularly in dogs, peak blood levels are achieved in 5-10 minutes, and the drug has totally disappeared from the bloodstream in a 2 hour period. The drug is not absorbed at all from the gastrointestinal tract of the dog, regardless of the dose.

Tissue distribution has been studied in the mouse, rat, cat, monkey, and dog. In all species, the drug was found to be markedly concentrated in the liver and kidney. The drug is retained in the liver of the dog for many hours after blood levels are undetectable.

It appears that less than 10% of streptozocin or its metabolites containing an N-nitroso group are excreted by the kidney. It has not been possible to evaluate biliary excretion with the methods available.

TOXICOLOGY

The toxicology of ZANOSAR (streptozocin) in experimental animals is a reflection of its therapeutic usefulness as an antineoplastic drug. Single and multiple parenteral doses administered to rodents, dogs and monkeys produced a diabetogenic state resembling human hyperglycemic diabetes mellitus. This occurred at single doses of 25 - 35 mg/kg in rats, dogs and monkeys and at multiple doses in the rat of 15 mg/kg/day for 31 days or 5 mg/kg weekly for 2 years.

Hepatotoxicity and nephrotoxicity were apparent in the dog and monkey studies along with other expected toxic signs including emesis, body weight loss, anorexia, muscle tremors, hypothermia and bradycardia in multiple dose dog studies.

ZANOSAR was found to be mutagenic *in vitro*, tumorigenic parenterally in rats (pancreas, kidney and genital organs) and hamsters (liver) and carcinogenic (lung) in mice. Topical administration of 10 mg/kg/week for up to 2 years to groups of 10 male and 10 female rats produced 2 benign skin tumors.

In reproduction studies in rats, there was an adverse effect on fertility with resultant altered estrous cycles, decreased fertility and increased prenatal death at the 16 mg/kg/day dose level. At 4 mg/kg/day and above, prolonged, difficult delivery and decreased postnatal survival were noted which were also noted in a peri-postnatal study during the last week of gestation at the same dose levels.

Treatment of rats throughout organogenesis at levels of 10 to 30 mg/kg/day resulted in decreased fetal body weights and a number of anomalies, however, none of the anomalies occurred in more than 1-fetus at any dose level or treatment interval.

Parenteral treatment of rabbits at dose levels of 5 to 20 mg/kg/day during organogenesis was not fetotoxic or teratogenic but there was an increased number of abortions and premature deliveries at the 20 mg/kg/day dose level.

Irritation studies conducted in rabbits and guinea pigs revealed that ZANOSAR is not an eye irritant nor a primary dermal irritant.

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