DRUG NAME: Streptozocin

SYNONYM(S): Streptozotocin[1]

COMMON TRADE NAME(S): ZANOSAR®

CLASSIFICATION: alkylating agent-antitumour antibiotic

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Streptozocin is a naturally occurring methylnitrosurea originally produced by fermentation of *Streptomyces achromogenes.* It is a nitrosurea that demonstrates specificity for beta and exocrine cells of the pancreas due to an attached sugar moiety. Streptozocin undergoes spontaneous decomposition to produce reactive methylcarbonium ions that alkylate DNA and cause interstrand cross links. Streptozocin inhibits the progression of cells into mitosis; however, since its cytotoxic action affects all phases of the cell cycle, streptozocin is cell cycle phase-nonspecific.[1,2]

PHARMACOKINETICS:

Oral Absorption	poorly absorbed, not active orally[2]	
Distribution	in animal models concentrates in the liver, kidney, intestine, and pancreas[2]	
	cross blood brain barrier?	no, metabolites: yes
	volume of distribution	43.8 L, average in a limited number of patients
	plasma protein binding	no information found
Metabolism	spontaneously degrades to methylcarbonium ions, extensively metabolized, likely in the liver and kidneys	
	active metabolite(s)	methylcarbonium ions, nitrosurea metabolites
	inactive metabolite(s)	yes
Excretion	primarily in the urine, drug and metabolites may be eliminated in expired air (<%5)	
	urine	60-70% within 24 h, 10% unchanged
	feces	<1%
	terminal half life	35-40 minutes
	clearance	478 mcg/min (range: 173-718 mcg/min)

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:

*Islet cell carcinoma of the pancreas

Other uses:

Carcinoid tumour[1]

Pancreatic adenoacarcinoma[1]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications[2]:

- history of hypersensitivity reaction to streptozocin
- pre-existing renal disease

Caution:

- renal toxicity may occur; renal function should be monitored regularly.[2,3]
- streptozocin should not be used with other potential nephrotoxins.[2]

Carcinogenicity: Streptozocin is carcinogenic in mice, rats, and hamsters. In rats, benign tumours have developed at the site of topical exposure; if contact with the skin or mucosa occurs, wash the affected areas immediately with soap and water.[2]

Mutagenicity: Streptozocin is mutagenic in bacteria, plants, and mammalian cells.[2]

Fertility: Streptozocin adversely affects fertility in male and female rats.[2] The effect of streptozocin on fertility in humans is not known.[1]

Pregnancy: FDA Pregnancy Category D.[4] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[5] When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow/ febrile neutropenia	myelosuppression (10-20%); may be cumulative, typically mild to moderate, deaths have occurred
	anemia
	eosinophilia; asymptomatic, resolves after treatment discontinuation
	leukopenia, neutropenia[4]; onset day 7, nadir days 7-14, recovery by day 21
	thrombocytopenia[4] (<1%); onset day 7, nadir days 7-14, recovery by day 21
constitutional symptoms	lethargy (<1%)[4]; only associated with continuous 5-day infusion
	fever (<1%)
dermatology/skin	*extravasation hazard:* vesicant[6]
	necrosis
endocrine	glucose intolerance; typically mild to moderate and reversible
	insulin shock (<1%); has occurred in patients with insulinomas, onset typically within 24 hours of therapy
	nephrogenic diabetes insipidus (<1%)
gastrointestinal	*emetogenic potential:* high[7]
	diarrhea (10%)[4]
	nausea/vomiting (~100%)[1]; onset typically 1-4 h following administration and may persist for 24 h, occasionally may require discontinuation of therapy, incidence and severity may be reduced with continuous 5-day infusion

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
hepatobiliary/pancreas	hepatotoxicity (<1%)[4]; deaths have occurred
metabolic/laboratory	elevated bilirubin and serum creatinine, proteinuria (>10%)[4]; may be associated with a Fanconi-like syndrome (glycosuria, acetonuria, and aminoaciduria)
	elevated BUN (>10%)[4]; transient
	elevated serum transaminases (25%); transient
	hyperchloremia
	hypoalbuminemia (>10%)[4]
	hypocalcemia
	hypoglycemia[4] (6%)
	hypokalemia
	hypophosphatemia (>10%)[4]
	renal tubular acidosis (>10%); may be associated with a Fanconi-like syndrome (glycosuria, acetonuria, and aminoaciduria)
neurology	confusion (<1%)[4]; only associated with continuous 5-day infusion
	depression (<1%)[4]; only associated with continuous 5-day infusion
pain	injection site pain (1-10%)[4]; typically following IV push
renal/genitourinary	***nephrotoxicity*** (25-75%)***;*** see paragraph following the **Side Effects** table

Adapted from standard reference[2] unless specified otherwise.

Nephrotoxicity is dose-limiting, cumulative, and may be severe, irreversible, or fatal. Hypophosphatemia and mild proteinuria may be the earliest signs of nephrotoxicity; increased BUN and serum creatinine concentrations typically develop later with continued treatment. Anuria, hyperchloremia, and proximal renal tubular acidosis, which may be associated with a Fanconi-like syndrome (glycosuria, acetonuria, and aminoaciduria), have occurred.Nephrogenic diabetes insipidus has rarely occurred. Delayed nephrotoxicity and renal failure have been reported following discontinuation of streptozocin. The risk of nephrotoxicity may be increased if streptozocin is administered intra-arterially. Renal function should be monitored regularly. Reduce the dose or discontinue therapy if nephrotoxicity occurs. The role of hydration in decreasing streptozocin-induced nephrotoxicity has not been clearly established.[1-3]

Glucose intolerance and hypoglycemia: Streptozocin is rarely diabetogenic, and mild to moderate glucose tolerance abnormalities have been reported; these are usually reversible.[1] However, a sudden release of insulin may occur initially, and hypoglycemia may result[4]; insulin shock with severe hypoglycemia has been reported.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
doxorubicin[1-3]	increased therapeutic and toxic effects of doxorubicin	increased elimination half-life of doxorubicin	monitor for toxicity; consider doxorubicin dose reduction
phenytoin[1,2]	decreased effect of streptozocin; single case report	unknown	avoid concomitant use

SUPPLY AND STORAGE:

Injection: Pfizer Canada Inc. supplies streptozocin as single use 1 g vials. Store in the refrigerator and protect from light.[2]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
Direct intravenous[1]	***into tubing of running IV; see Prevention and Management of Extravasation of Chemotherapy***
Intermittent infusion[1]	***over 15 minutes to 6 hours***
Continuous infusion[2]	has been used; may be associated with increased CNS toxicity
Intraperitoneal[8]	investigational
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial[1,2]	investigational; not recommended due to increased risk of nephrotoxicity
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***6 weeks***[2,3]:	***500 mg/m^2 IV once daily for 5 consecutive days starting on day 1*** ***(total dose per cycle 2500 mg/m^2)*** • continuous infusions have also been used

BCCA usual dose noted in ***bold, italics***

Cycle Length:

1 week[2]: 1000 mg/m^2 (range 1000-1500 mg/m^2) IV for one dose on day 1
(total dose per cycle 1000 mg/m^2 [range 1000-1500 mg/m^2])

- dose escalation above 1000 mg/m^2 should not occur prior to cycle 3

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure:

- the effect of renal impairment on streptozocin pharmacokinetics has not been evaluated[1]
- dose reduce or discontinue therapy if significant renal toxicity occurs[2]
- the following guidelines have been used[1]:

Creatinine clearance (mL/min)	Dose
10-50	75%
<10	50%

Calculated creatinine clearance = $\frac{\text{N* x (140 - Age) x weight in kg}}{\text{Serum Creatinine in µmol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: dose reduce or discontinue therapy if significant hepatic toxicity occurs[2]; no specific guidelines found

Dosage in dialysis: no information found

Children: no information found

REFERENCES:

1. McEvoy GK, editor. AHFS 2007 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1180-1184.
2. Pfizer Canada Inc. ZANOSAR™ product monograph. 08 October 2003.
3. BC Cancer Agency Gastrointestinal Tumour Group. (GIENDO2) BCCA Protocol Summary for Palliative Therapy for Pancreatic Endocrine Tumours using Streptozocin and Doxorubicin. Vancouver, British Columbia: BC Cancer Agency; 1 July 2006.
4. Rose BD editor. Streptozocin. www.uptodate.com ed. Waltham, Massachusetts: UpToDate 15.2; 2007.
5. Sharlene Gill MD. Personal communication - Streptozocin. BC Cancer Agency Gastrointestinal Tumour Group.; 1 August 2007.
6. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 September 2006.
7. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 November 2005.
8. Goel R, McClay EF, Kirmani S, et al. Pharmacokinetics study of intraperitoneal streptozotocin. Clinical & Investigative Medicine 1992;15(5):420-426.