Hexalen (Altretamine) Capsules Prescribing Information

• WARNINGS (boxed)

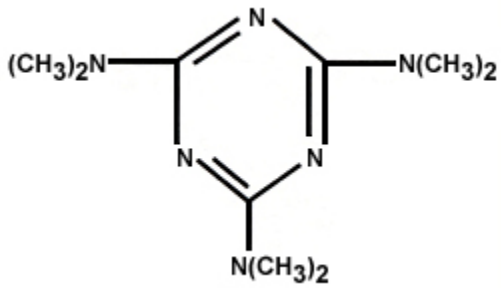
IMPORTANT: This document contains information intended for healthcare professionals only. This material is not intended for use by non-healthcare professionals.

WARNINGS

1. HEXALEN® should only be given under the supervision of a physician experienced in the use of antineoplastic agents.
2. Peripheral blood counts should be monitored at least monthly, prior to the initiation of each course of HEXALEN, and as clinically indicated (see Adverse Reactions).
3. Because of the possibility of HEXALEN-related neurotoxicity, neurologic examination should be performed regularly during HEXALEN administration (see Adverse Reactions).

DESCRIPTION

HEXALEN (altretamine), is a synthetic cytotoxic antineoplastic s-triazine derivative. HEXALEN capsules contain 50 mg of altretamine for oral administration. Inert ingredients include lactose, anhydrous and calcium stearate. Altretamine, known chemically as N,N,N',N",N"-hexamethyl-1,3,5-triazine-2,4,6-triamine, has the following structural formula:



Its empirical formula is C9H18N6 with a molecular weight of 210.28. Altretamine is a white crystalline powder, melting at 172°± 1°C. Altretamine is practically insoluble in water but is increasingly soluble at pH 3 and below.

CLINICAL PHARMACOLOGY

The precise mechanism by which HEXALEN exerts its cytotoxic effect is unknown, although a number of theoretical possibilities have been studied. Structurally, HEXALEN resembles the alkylating agent triethylenemelamine, yet in vitro tests for alkylating activity of HEXALEN and its metabolites have been negative. HEXALEN has been demonstrated to be efficacious for certain ovarian tumors resistant to classical alkylating agents. Metabolism of altretamine is a requirement for cytotoxicity. Synthetic monohydroxymethylmelamines, and products of altretamine metabolism, in vitro and in vivo, can form covalent adducts with tissue macromolecules including DNA, but the relevance of these reactions to antitumor activity is unknown.

HEXALEN is well-absorbed following oral administration in humans, but undergoes rapid and extensive demethylation in the liver, producing variation in altretamine plasma levels. The principal metabolites are pentamethylmelamine and tetramethylmelamine.

Pharmacokinetic studies were performed in a limited number of patients and should be considered preliminary. After oral administration of HEXALEN to 11 patients with advanced ovarian cancer in doses of 120-300 mg/m ^{2}, peak plasma levels (as measured by gas-chromatographic assay) were reached between 0.5 and 3 hours, varying from 0.2 to 20.8 mg/l. Half-life of the ß-phase of emination ranged from 4.7 to 10.2 hours. Altretamine and metabolites show binding to plasma proteins. The free fractions of altretamine, pentamethylmelamine and tetramethylmelamine are 6%, 25% and 50%, respectively.

Following oral administration of ^{14}C-ring-labeled altretamine (4 mg/kg), urinary recovery of radioactivity was 61% at 24 hours and 90% at 72 hours. Human urinary metabolites were N-demethylated homologues of altretamine with <1% unmetabolized altretamine excreted at 24 hours.

After intraperitoneal administration of ^{14}C-ring-labeled altretamine to mice, tissue distribution was rapid in all organs, reaching a maximum at 30 minutes. The excretory organs (liver and kidney) and the small intestine showed high concentrations of radioactivity, whereas relatively low concentrations were found in other organs, including the brain.

There have been no formal pharmacokinetic studies in patients with compromised hepatic and/or renal function, though HEXALEN has been administered both concurrently and following nephrotoxic drugs such as cisplatin.

HEXALEN (altretamine) has been administered in 4 divided doses, with meals and at bedtime, though there is no pharmacokinetic data on this schedule nor information from formal interaction studies about the effect of food on its bioavailability or pharmacokinetics.

In two studies in patients with persistent or recurrent ovarian cancer following first-line treatment with cisplatin and/or alkylating agent-based combinations, HEXALEN was administered as a single agent for 14 or 21 days of a 28 day cycle. In the 51 patients with measurable or evaluable disease, there were 6 clinical complete responses, 1 pathologic complete response, and 2 partial responses for an overall response rate of 18%. The duration of these responses ranged from 2 months in a patient with a palpable pelvic mass to 36 months in a patient who achieved a pathologic complete response. In some patients, tumor regression was associated with improvement in symptoms and performance status.

INDICATIONS and USAGE

HEXALEN is indicated for use as a single agent in the palliative treatment of patients with persistent or recurrent ovarian cancer following first-line therapy with a cisplatin and/or alkylating agent-based combination.

CONTRAINDICATIONS

HEXALEN is contraindicated in patients who have shown hypersensitivity to it. HEXALEN should not be employed in patients with preexisting severe bone marrow depression or severe neurologic toxicity. HEXALEN has been administered safely, however, to patients heavily pretreated with cisplatin and/or alkylating agents, including patients with preexisting cisplatin neuropathies.Careful monitoring of neurologic function in these patients is essential.

WARNINGS

See boxed Warnings.

Concurrent administration of HEXALEN and antidepressants of the monoamine oxidase (MAO) inhibitor class may cause severe orthostatic hypotension.Four patients, all over 60 years of age, were reported to have experienced symptomatic hypotension after 4 to 7 days of concomitant therapy with HEXALEN and MAO inhibitors.

HEXALEN causes mild to moderate myelosuppression and neurotoxicity. Blood counts and a neurologic examination should be performed prior to the initiation of each course of therapy and the dose of HEXALEN adjusted as clinically indicated (see Dosage and Administration).

Pregnancy: Category D

HEXALEN has been shown to be embryotoxic and teratogenic in rats and rabbits when given at doses 2 and 10 times the human dose. HEXALEN may cause fetal damagewhen administered to a pregnant woman. If HEXALEN is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General

Neurologic examination should be performed regularly (see Adverse Reactions).

Laboratory Tests

Peripheral blood counts should be monitored at least monthly, prior to the initiation of each course of HEXALEN, and as clinically indicated (see Adverse Reactions).

Drug Interactions

Concurrent administration of HEXALEN and antidepressants of the MAO inhibitor class may cause severe orthostatic hypotension (see Warnings section). Cimetidine, an inhibitor of microsomal drug metabolism, increased altretamine's half-life and toxicity in a rat model.

Data from a randomized trial of HEXALEN and cisplatin plus or minus pyridoxine in ovarian cancer indicated that pyridoxine significantly reduced neurotoxicity; however, it adversely affected response duration suggesting that pyridoxine should not be administered with HEXALEN and/or cisplatin (1).

Carcinogenesis, Mutagenesis and Impairment of Fertility

The carcinogenic potential of HEXALEN has not been studied in animals, but drugs with similar mechanisms of action have been shown to be carcinogenic. HEXALEN was weakly mutagenic when tested in strain TA100 of *Salmonella typhimurium*. HEXALEN administered to female rats 14 days prior to breeding through the gestation period had no adverse effect on fertility, but decreased post-natal survival at 120 mg/m^2/day and was embryocidal at 240 mg/m^2/day. Administration of 120 mg/m^2/day HEXALEN to male rats for 60 days prior to mating resulted in testicular atrophy, reduced fertility and a possible dominant lethal mutagenic effect. Male rats treated with HEXALEN at 450 mg/m^2/day for 10 days had decreased spermatogenesis, atrophy of testes, seminal vesicles and ventral prostate.

Pregnancy

Pregnancy Category D: see Warnings section.

Nursing Mothers

It is not known whether altretamine is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to HEXALEN treatment of the mother, it is recommended that breast feeding be discontinued if the mother is treated with HEXALEN.

Pediatric Use

The safety and effectiveness of HEXALEN in children have not been established.

ADVERSE REACTIONS

Gastrointestinal

With continuous high-dose daily HEXALEN, nausea and vomiting of gradual onset occur frequently. Although in most instances these symptoms are controllable with anti-emetics, at times the severity requires HEXALEN dose reduction or, rarely, discontinuation of HEXALEN therapy. In some instances, a tolerance of these symptoms develops after several weeks of therapy. The incidence and severity of nausea and vomiting are reduced with moderate-dose administration of HEXALEN.

In 2 clinical studies of single-agent HEXALEN utilizing a moderate, intermittent dose and schedule, only 1 patient (1%) discontinued HEXALEN due to severe nausea and vomiting.

Neurotoxicity

Peripheral neuropathy and central nervous system symptoms (mood disorders, disorders of consciousness, ataxia, dizziness, vertigo) have been reported. They are more likely to occur in patients receiving continuous high-dose daily HEXALEN (altretamine) than moderate-dose HEXALEN administered on an intermittent schedule. Neurologic toxicity has been reported to be reversible when therapy is discontinued. Data from a randomized trial of HEXALEN and cisplatin plus or minus pyridoxine in ovarian cancer indicated that pyridoxine significantly reduced eurotoxicity; however, it adversely affected response duration suggesting that pyridoxine should not be administered with HEXALEN and/or cisplatin (1).

Hematologic

HEXALEN causes mild to moderate dose-related myelosuppression. Leukopenia below 3000 WBC/mm^3 occurred in <15% of patients on a variety of intermittent or continuous dose regimens. Less than 1% had leukopenia below 1000 WBC/mm^3. Thrombocytopenia below 50,000 platelets/mm^3 was seen in <10% of patients. When given in doses of 8-12 mg/kg/day over a 21 day course, nadirs of leukocyte and platelet counts were reached by 3-4 weeks, and normal counts were regained by 6 weeks. With continuous administration at doses of 6-8 mg/kg/day, nadirs are reached in 6-8 weeks (median).

Data in the following table are based on the experience of 76 patients with ovarian cancer previously treated with a cisplatin-based combination regimen who received single-agent HEXALEN. In one study, HEXALEN, 260 mg/m^2/day, was administered for 14 days of a 28 day cycle. In another study, HEXALEN, 6-8 mg/kg/day, was administered for 21 days of a 28 day cycle.

Adverse Experiences in 76 Previously Treated Ovarian Cancer Patients Receiving Single-Agent HEXALEN

Adverse Experiences	**% Patients**
Gastrointestinal	
Nausea and Vomiting	33
Mild to Moderate	32
Severe	1
Increased Alkaline Phosphatase	9
Neurologic	
Peripheral Sensory Neuropathy	31
Mild	22
Moderate to Severe	9
Anorexia and Fatigue	1
Seizures	1
Hematologic	
Leukopenia	5
WBC 2000-2999/mm^3	4
WBC <2000/mm^3	1
Thrombocytopenia	9
Platelets 75,000-99,000/mm^3	6
Platelets <75,000/mm^3	3
Anemia	33
Mild	20
Moderate to Severe	13

Renal		
Serum Creatinine 1.6-3.75 mg/dl		7
BUN		9
	25-40 mg%	5
	41-60 mg%	3
	>60 mg%	1

Additional adverse reaction information is available from 13 single-agent altretamine studies (total of 1014 patients) conducted under the auspices of the National Cancer Institute. The treated patients had a variety of tumors and many were heavily pretreated with other chemotherapies; most of these trials utilized high, continuous daily doses of altretamine (6-12 mg/kg/day). In general, adverse reaction experiences were similar in the two trials described above. Additional toxicities, not reported in the above table, included hepatic toxicity, skin rash, pruritus and alopecia, each occurring in <1% of patients.

OVERDOSAGE

No case of acute overdosage in humans has been described. The oral LD50 dose in rats was 1050 mg/kg and 437 mg/kg in mice.

DOSAGE AND ADMINISTRATION

HEXALEN (altretamine) is administered orally.Doses are calculated on the basis of bodysurface area.

HEXALEN may be administered either for 14 or 21 consecutive days in a 28 day cycle at a dose of 260 mg/m^2/day. The total daily dose should be given as 4 divided oral doses after meals and at bedtime. There is no pharmacokinetic information supporting this dosing regimen and the effect of food on HEXALEN bioavailability or pharmacokinetics has not been evaluated.

HEXALEN should be temporarily discontinued (for 14 days or longer) and subsequently restarted at 200 mg/m^2/day for any of the following situations:

1) Gastrointestinal intolerance unresponsive to symptomatic measures;
2) White blood count <2000/mm^3 or granulocyte count <1000/mm^3;
3) Platelet count <75,000/mm^3;
4) Progressive neurotoxicity.

If neurologic symptoms fail to stabilize on the reduced dose schedule, HEXALEN should be discontinued indefinitely.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published (2-8). There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

HEXALEN is available in 50 mg clear, hard gelatin capsules imprinted with the following inscription: USB 001.

Bottles of 100 capsules (NDC 58063-0001-70)

Store at controlled room temperature 15° to 30°C (59° to 86°F).

REFERENCES

1. Wiernik PH, et al. Hexamethylmelamine and Low or Moderate Dose Cisplatin With or Without Pyridoxine for Treatment of Advanced Ovarian Carcinoma: A Study of the Eastern Cooperative Oncology Group. Cancer Investigation 10(1): 1-9, 1992.

2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No.83-2621. For sale by the Superintendent of Documents, U.S. Government Printing

Office, Washington, D.C. 20402.

3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. Journal of the American Medical Association March 15, 1985.

4. National Study Commission on Cytotoxic Exposure - Recommendation for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Director of Pharmacy Services, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.

5. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Medical Journal of Australia 1:426-428, 1983.

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7. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic Drugs in Hospitals. American Journal of Hospital Pharmacy 42:131-137, 1985.

8. OSHA Work Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. American Journal of Hospital Pharmacy 43:1193-1204, 1986.