

Male patients who are sexually active with female partners who are or may become pregnant should use a condom during and for at least 4 months after treatment.

Infertility

Females

Amenorrhea, transient or permanent, associated with decreased estrogen and increased gonadotropin secretion develops in a proportion of women treated with cyclophosphamide. Affected patients generally resume regular menses within a few months after cessation of therapy. The risk of premature menopause with cyclophosphamide increases with age. Oligomenorrhea has also been reported in association with cyclophosphamide treatment.

Animal data suggest an increased risk of failed pregnancy and malformations may persist after discontinuation of cyclophosphamide as long as oocytes/follicles exist that were exposed to cyclophosphamide during any of their maturation phases. The exact duration of follicular development in humans is not known, but may be longer than 12 months [see *Nonclinical Toxicology* (13.1)].

Males

Men treated with cyclophosphamide may develop oligospermia or azoospermia which are normally associated with increased gonadotropin but normal testosterone secretion.

8.7 Use in Patients with Renal Impairment

In patients with severe renal impairment, decreased renal excretion may result in increased plasma levels of cyclophosphamide and its metabolites. This may result in increased toxicity [see *Clinical Pharmacology* (12.3)]. Monitor patients with severe renal impairment (CrCl =10 mL/min to 24 mL/min) for signs and symptoms of toxicity.

Cyclophosphamide and its metabolites are dialyzable although there are probably quantitative differences depending upon the dialysis system being used. In patients requiring dialysis, use of a consistent interval between cyclophosphamide administration and dialysis should be considered.

8.8 Use in Patients with Hepatic Impairment

Patients with severe hepatic impairment have reduced conversion of cyclophosphamide to the active 4-hydroxyl metabolite, potentially reducing efficacy [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

No specific antidote for cyclophosphamide is known.

Overdosage should be managed with supportive measures, including appropriate treatment for any concurrent infection, myelosuppression, or cardiac toxicity should it occur.

Serious consequences of overdosage include manifestations of dose dependent toxicities such as myelosuppression, urotoxicity, cardiotoxicity (including cardiac failure), veno-occlusive hepatic disease, and stomatitis [see *Warnings and Precautions* (5.1, 5.2, 5.3 and 5.6)].

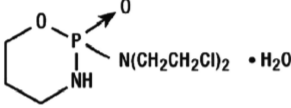
Patients who received an overdose should be closely monitored for the development of toxicities, and hematologic toxicity in particular.

Cyclophosphamide and its metabolites are dialyzable. Therefore, rapid hemodialysis is indicated when treating any suicidal or accidental overdose or intoxication.

Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects with cyclophosphamide overdose.

11 DESCRIPTION

Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. The chemical name for cyclophosphamide is 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, and has the following structural formula:



Cyclophosphamide is a white crystalline powder with the molecular formula C₇H₁₅Cl₂N₂O₂P•H₂O and a molecular weight of 279.1. Cyclophosphamide is soluble in water, saline, or ethanol.

Cyclophosphamide for Injection, USP is for intravenous or oral use, it has no inactive ingredients. When reconstituted in water Cyclophosphamide for Injection, USP has a pH range of 3.0 to 9.0.

Cyclophosphamide for Injection, USP is a sterile white powder available as 500 mg, 1 g, and 2 g strength vials.

- 500 mg vial contains 534.5 mg cyclophosphamide monohydrate equivalent to 500 mg cyclophosphamide
- 1 g vial contains 1069.0 mg cyclophosphamide monohydrate equivalent to 1 g cyclophosphamide
- 2 g vial contains 2138.0 mg cyclophosphamide monohydrate equivalent to 2 g cyclophosphamide

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action is thought to involve cross-linking of tumor cell DNA.

12.2 Pharmacodynamics

Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells.

12.3 Pharmacokinetics

Following IV administration, elimination half-life (t_{1/2}) ranges from 3 to 12 hours with total body clearance (CL) values of 4 to 5.6 L/h. Pharmacokinetics are linear over the dose range used clinically. When cyclophosphamide was administered at 4.0 g/m² over a 90 minutes infusion, saturable elimination in parallel with first-order renal elimination describe the kinetics of the drug.

Absorption

After oral administration, peak concentrations of cyclophosphamide occurred at one hour. Area under the curve ratio for the drug after oral and IV administration (AUC_{0-∞}: AUC_∞) ranged from 0.87 to 0.96.

Distribution

Approximately 20% of cyclophosphamide is protein bound, with no dose dependent changes. Some metabolites are protein bound to an extent greater than 60%. Volume of distribution approximates total body water (30 to 50 L).

Metabolism

The liver is the major site of cyclophosphamide activation. Approximately 75% of the administered dose of cyclophosphamide is activated by hepatic microsomal cytochrome P450s including CYP2A6, 2B6, 3A4, 3A5, 2C9, 2C18 and 2C19, with 2B6 displaying the highest 4-hydroxylase activity. Cyclophosphamide is activated to form 4-hydroxycyclophosphamide, which is in equilibrium with its ring-open tautomer aldophosphamide. 4-hydroxycyclophosphamide and aldophosphamide can undergo oxidation by aldehyde dehydrogenases to form the inactive metabolites 4-ketocyclophosphamide and carboxyphosphamide, respectively. Aldophosphamide can undergo β-elimination to form active metabolites phosphoramidate mustard and acrolein. This spontaneous conversion can be catalyzed by albumin and other proteins. Less than 5% of cyclophosphamide may be directly detoxified by side chain oxidation, leading to the formation of inactive metabolites 2-dechloroethylcyclophosphamide. At high doses, the fraction of parent compound cleared by 4-hydroxylation is reduced resulting in non-linear elimination of cyclophosphamide in patients. Cyclophosphamide appears to induce its own metabolism. Auto-induction results in an increase in the total clearance, increased formation of 4-hydroxyl metabolites and shortened t_{1/2} values following repeated administration at 12- to 24-hour interval.

Elimination

Cyclophosphamide is primarily excreted as metabolites. 10 to 20% is excreted unchanged in the urine and 4% is excreted in the bile following IV administration.

Special Populations

Renal Impairment

The pharmacokinetics of cyclophosphamide were determined following one-hour intravenous infusion to renally impaired patients. The results demonstrated that the systemic exposure to cyclophosphamide increased as the renal function decreased. Mean dose-corrected AUC increased by 38% in the moderate renal group, (Creatinine clearance (CrCl of 25 to 50 mL/min), by 64% in the severe renal group (CrCl of 10 to 24 mL/min) and by 23% in the hemodialysis group (CrCl of < 10 mL/min) compared to the control group. The increase in exposure was significant in the severe group (p>0.05); thus, patients with severe renal impairment should be closely monitored for toxicity [see *Use in Specific Populations* (8.7)].

The dialyzability of cyclophosphamide was investigated in four patients on long-term hemodialysis. Dialysis clearance calculated by arterial-venous difference and actual drug recovery in dialysate averaged 104 mL/min, which is in the range of the metabolic clearance of 95 mL/min for the drug. A mean of 37% of the administered dose of cyclophosphamide was removed during hemodialysis. The elimination half-life (t_{1/2}) was 3.3 hours in patients during hemodialysis, a 49% reduction of the 6.5 hours to t_{1/2} reported in uremic patients. Reduction in t_{1/2}, larger dialysis clearance than metabolic clearance, high extraction efficiency, and significant drug removal during dialysis, suggest that cyclophosphamide is dialyzable.

Hepatic Impairment

Total body clearance (CL) of cyclophosphamide is decreased by 40% in patients with severe hepatic impairment and elimination half-life (t_{1/2}) is prolonged by 64%. Mean CL and t_{1/2} were 45 ± 8.6 L/kg and 12.5 ± 1.0 hours respectively, in patients with severe hepatic impairment and 63 ± 7.6 L/kg and 7.6 ± 1.4 hours respectively in the control group [see *Use in Specific Populations* (8.8)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Cyclophosphamide administered by different routes, including intravenous, subcutaneous or intraperitoneal injection, or in drinking water, caused tumors in both mice and rats. In addition to leukemia and lymphoma, benign and malignant tumors were found at various tissue sites, including urinary bladder, mammary gland, lung, liver, and injection site [see *Warnings and Precautions* (5.5)].

Cyclophosphamide was mutagenic and clastogenic in multiple *in vitro* and *in vivo* genetic toxicology studies.

Cyclophosphamide is genotoxic in male and female germ cells. Animal data indicate that exposure of oocytes to cyclophosphamide during follicular development may result in a decreased rate of implantations and viable pregnancies, and in an increased risk of malformations. Male mice and rats treated with cyclophosphamide show alterations in male reproductive organs (e.g., decreased weights, atrophy, changes in spermatogenesis), and decreases in reproductive potential (e.g., decreased implantations and increased post-implantation loss) and increases in fetal malformations when mated with untreated females [see *Use in Specific Populations* (8.6)].

15 REFERENCES

1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cyclophosphamide for Injection, USP is a sterile white powder containing cyclophosphamide and is supplied in vials for single dose use.

Product Code	Unit of Sale	Strength
123135	NDC 65219-135-20 Individually packaged	500 mg/vial
123131	NDC 65219-131-20 Individually packaged	1 g/vial
123132	NDC 65219-133-20 Individually packaged	2 g/vial

Store vials at or below 25°C (77°F). During transport or storage of cyclophosphamide vials, temperature influences can lead to melting of the active ingredient, cyclophosphamide [see *Dosage and Administration* (2.3)].

Cyclophosphamide is an antineoplastic product. Follow special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Advise the patient of the following:

- Inform patients of the possibility of myelosuppression, immunosuppression, and infections. Explain the need for routine blood cell counts. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever [see *Warnings and Precautions* (5.1)].
- Advise the patient to report urinary symptoms (patients should report if their urine has turned a pink or red color) and the need for increasing fluid intake and frequent voiding [see *Warnings and Precautions* (5.2)].
- Advise patients to contact a healthcare professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [see *Warnings and Precautions* (5.3)].
- Warn patients of the possibility of developing non-infectious pneumonitis. Advise patients to report promptly any new or worsening respiratory symptoms [see *Warnings and Precautions* (5.4)].
- Advise female patients of reproductive potential to use highly effective contraception during treatment and for up to 1 year after completion of therapy. There is a potential for harm to a fetus if a patient becomes pregnant during this period. Patients should immediately contact their healthcare provider if they become pregnant or if pregnancy is suspected during this period [see *Warnings and Precautions* (5.7) and *Use in Specific Populations* (8.1)].
- Advise male patients who are sexually active with a female partner who is or may become pregnant to use condoms during treatment and for up to 4 months after completion of therapy. There is a potential for harm to a fetus if a patient fathers a child during this period. Patients should immediately contact their healthcare provider if their female partner becomes pregnant or if pregnancy is suspected during this period [see *Warnings and Precautions* (5.7) and *Use in Specific Populations* (8.1)].
- Advise nursing mothers treated with cyclophosphamide to discontinue nursing or discontinue cyclophosphamide, taking into account the importance of the drug to the mother [see *Use in Specific Populations* (8.3)].
- Explain to patients that side effects such as nausea, vomiting, stomatitis, impaired wound healing, amenorrhea, premature menopause, sterility and hair loss may be associated with cyclophosphamide administration. Other undesirable effects (including, e.g., dizziness, blurred vision, visual impairment) could affect the ability to drive or use machines [see *Adverse Reactions* (6.1 and 6.2)].