# CYCLOPHOSPHAMIDE INJECTION

## Ordering Information[1]

To order AVYXA CYCLOPHOSPHAMIDE INJECTION 500 mg/mL, please contact one of these authorized specialty distributors and use the appropriate order number:


**500 mg/mL**
**NDC: 83831-116-01**


**1 gram/2 mL (500 mg/mL)**
**NDC: 83831-117-02**


**2 gram/4 mL (500 mg/mL)**
**NDC: 83831-118-04**

| Institutions/Hospitals | 500 mg | 1 gram | 2 gram |
|---|---|---|---|
| **Cardinal Health Specialty** | 5932074 | 5932082 | 5932090 |
| **CENCORA - ASD Healthcare** | 10290770 | 10290771 | 10290773 |
| **McKesson Plasma & Biologics** | 2977437 | 2977387 | 2977411 |
| **Physician Offices** | **500 mg** | **1 gram** | **2 gram** |
| **Cardinal Health Specialty** | 5932074 | 5932082 | 5932090 |
| **Oncology Supply** | 10290761 | 10290762 | 10290767 |
| **McKesson Specialty Health** | 5018103 | 5018104 | 5018105 |

## Highlights[1]

- No reconstitution is required and ready to dilute solution
- Ready to add to direct intravenous injection with;
  - 0.9% Sodium Chloride Injection, USP
- Ready to add to the intravenous infusion solution with different options;
  - 0.45% Sodium Chloride Injection, USP
  - 5% Dextrose Injection, USP
  - 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- Not made with natural rubber

UNIQUE
J-CODE
**J9072**

**Please see full Prescribing Information for CYCLOPHOSPHAMIDE INJECTION.**

AVYXASSIST™

## Simplifying Patient Access, Providing Comprehensive Support.

**AVYXASSIST™can offer support to qualifying patients in need. The program provides the following services***

- Benefit verification
- Prior authorization requirements
- Appeals process information
- Referrals to 501(c)(3) foundations when applicable
- Free product assistance (uninsured or underinsured), bridge supply (coverage delays)
- Product replacement
- Copay assistance

### COPAY ASSISTANCE PROGRAM

Eligible patients may pay as little as **$0** per dose*

## TO ENROLL, PLEASE CHOOSE ONE OF THE FOLLOWING OPTIONS

### Phone

866-939-8927
Monday through Friday
8 AM to 8 PM ET

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OR

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Click on the link below to begin your online enrollment

ENROLL NOW

OR

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Download, print and fax the completed enrollment form to 833-852-3420

DOWNLOAD NOW

*For Eligibility Requirements Please Contact A Patient Access Specialist. Terms And Conditions Apply.

# INDICATIONS AND IMPORTANT SAFETY INFORMATION

## INDICATIONS

Malignant Diseases

CYCLOPHOSPHAMIDE INJECTION is indicated for the treatment of adult and pediatric patients with:

- malignant lymphomas (Stages III and IV of the Ann Arbor staging system), Hodgkin's disease, lymphocytic lymphoma (nodular or diffuse), mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma
- multiple myeloma
- leukemias: chronic lymphocytic leukemia, chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis), acute myelogenous and monocytic leukemia, acute lymphoblastic (stem-cell) leukemia (cyclophosphamide given during remission is effective in prolonging its duration)
- mycosis fungoides (advanced disease)
- neuroblastoma (disseminated disease)
- adenocarcinoma of the ovary
- retinoblastoma
- carcinoma of the breast

CYCLOPHOSPHAMIDE INJECTION, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs.

## IMPORTANT SAFETY INFORMATION

### DOSAGE AND ADMINISTRATION

**Important Dosing Information**

During or immediately after the administration, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity. Therefore, CYCLOPHOSPHAMIDE INJECTION should be administered in the morning.

### CONTRAINDICATIONS

Hypersensitivity

CYCLOPHOSPHAMIDE INJECTION is contraindicated in patients who have a history of severe hypersensitivity reactions to it, any of its metabolites, or to other components of the product. Anaphylactic reactions including death have been reported with cyclophosphamide. Possible cross-sensitivity with other alkylating agents can occur.

Urinary Outflow Obstruction

CYCLOPHOSPHAMIDE INJECTION is contraindicated in patients with urinary outflow obstruction.

# IMPORTANT SAFETY INFORMATION (CONTINUED)

## WARNINGS AND PRECAUTIONS

### Myelosuppression, Immunosuppression, Bone Marrow Failure and Infections

Cyclophosphamide can cause myelosuppression (leukopenia, neutropenia, thrombocytopenia and anemia), bone marrow failure, and severe immunosuppression which may lead to serious and sometimes fatal infections, including sepsis and septic shock. Latent infections can be reactivated.

Antimicrobial prophylaxis may be indicated in certain cases of neutropenia at the discretion of the managing physician. In case of neutropenic fever, antibiotic therapy is indicated. Antimycotics and/or antivirals may also be indicated.

Monitoring of complete blood counts is essential during cyclophosphamide treatment so that the dose can be adjusted, if needed. Cyclophosphamide Injection should not be administered to patients with neutrophils ≤1,500/$mm^3$ and platelets < 50,000/$mm^3$. Cyclophosphamide Injection treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop a serious infection. G-CSF may be administered to reduce the risks of neutropenia complications associated with cyclophosphamide use. Primary and secondary prophylaxis with G-CSF should be considered in all patients considered to be at increased risk for neutropenia complications. The nadirs of the reduction in leukocyte count and thrombocyte count are usually reached in weeks 1 and 2 of treatment. Peripheral blood cell counts are expected to normalize after approximately 20 days. Bone marrow failure has been reported. Severe myelosuppression may be expected particularly in patients pretreated with and/or receiving concomitant chemotherapy and/or radiation therapy.

### Urinary Tract and Renal Toxicity

Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported with cyclophosphamide. Medical and/or surgical supportive treatment may be required to treat protracted cases of severe hemorrhagic cystitis. Discontinue Cyclophosphamide Injection therapy in case of severe hemorrhagic cystitis. Urotoxicity (bladder ulceration, necrosis, fibrosis, contracture and secondary cancer) may require interruption of Cyclophosphamide Injection treatment or cystectomy. Urotoxicity can be fatal. Urotoxicity can occur with short-term or long-term use of cyclophosphamide.

Before starting treatment, exclude or correct any urinary tract obstructions. Urinary sediment should be checked regular for the presence of erythrocytes and other signs of urotoxicity and/or nephrotoxicity. Cyclophosphamide Injection should be used with caution, if at all, in patients with active urinary tract infections. Aggressive hydration with forced diuresis and frequent bladder emptying can reduce the frequency and severity of bladder toxicity. Mesna has been used to prevent severe bladder toxicity.

### Cardiotoxicity

Myocarditis, myopericarditis, pericardial effusion including cardiac tamponade, and congestive heart failure, which may be fatal, have been reported with cyclophosphamide therapy.

Supraventricular arrhythmias (including atrial fibrillation and flutter) and ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported after treatment with regimens that included cyclophosphamide.

The risk of cardiotoxicity may be increased with high doses of cyclophosphamide, in patients with advanced age, and in patients with previous radiation treatment to the cardiac region and/or previous or concomitant treatment with other cardiotoxic agents.

Particular caution is necessary in patients with risk factors for cardiotoxicity and in patients with preexisting cardiac disease.

Monitor patients with risk factors for cardiotoxicity and with pre-existing cardiac disease.

# IMPORTANT SAFETY INFORMATION (CONTINUED)

## Pulmonary Toxicity

Pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease and other forms of pulmonary toxicity leading to respiratory failure have been reported during and following treatment with cyclophosphamide. Late onset pneumonitis (greater than 6 months after start of cyclophosphamide) appears to be associated with increased mortality. Pneumonitis may develop years after treatment with cyclophosphamide.

Monitor patients for signs and symptoms of pulmonary toxicity.

## Secondary Malignancies

Cyclophosphamide is genotoxic. Secondary malignancies (urinary tract cancer, myelodysplasia, acute leukemias, lymphomas, thyroid cancer, and sarcomas) have been reported in patients treated with cyclophosphamide-containing regimens. The risk of bladder cancer may be reduced by prevention of hemorrhagic cystitis.

## Veno-occlusive Liver Disease

Veno-occlusive liver disease (VOD) including fatal outcome has been reported in patients receiving cyclophosphamide-containing regimens. A cytoreductive regimen in preparation for bone marrow transplantation that consists of cyclophosphamide in combination with whole-body irradiation, busulfan, or other agents has been identified as a major risk factor. VOD has also been reported to develop gradually in patients receiving long-term low-dose immunosuppressive doses of cyclophosphamide.

Other risk factors predisposing to the development of VOD include preexisting disturbances of hepatic function, previous radiation therapy of the abdomen, and a low performance status.

## Alcohol Content

The alcohol content in a dose of Cyclophosphamide Injection may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in Cyclophosphamide Injection on the ability to drive or use machines immediately after the infusion.

Each administration of Cyclophosphamide Injection at 50 mg per kg delivers 0.0448 g/kg of ethanol. For a 75 kg patient this would deliver 3.36 grams of ethanol. Other cyclophosphamide products may have a different amount of alcohol or no alcohol.

## Embryo-Fetal Toxicity

Based on its mechanism of action and published reports of effects in pregnant patients or animals, Cyclophosphamide Injection can cause fetal harm when administered to a pregnant woman. Exposure to cyclophosphamide during pregnancy may cause birth defects, miscarriage, fetal growth retardation, and fetotoxic effects in the newborn. Cyclophosphamide is teratogenic and embryo-fetal toxic in mice, rats, rabbits and monkeys.

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with Cyclophosphamide Injection and for up to 1 year after completion of therapy. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Cyclophosphamide Injection and for 4 months after completion of therapy.

**Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for CYCLOPHOSPHAMIDE INJECTION.**

# IMPORTANT SAFETY INFORMATION (CONTINUED)

### Infertility

Male and female reproductive function and fertility may be impaired in patients being treated with Cyclophosphamide Injection. Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Development of sterility appears to depend on the dose of cyclophosphamide, duration of therapy, and the state of gonadal function at the time of treatment. Cyclophosphamide induced sterility may be irreversible in some patients. Advise patients on the potential risks for infertility.

### Impairment of Wound Healing

Cyclophosphamide may interfere with normal wound healing

### Hyponatremia

Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome resembling SIADH (syndrome of inappropriate secretion of antidiuretic hormone), which may be fatal, has been reported.

## ADVERSE REACTIONS

Please see “Warnings and Precautions, Contraindications, and Use in Specific Populations” for more information on the following adverse reactions:

- Hypersensitivity
- Myelosuppression, Immunosuppression, Bone Marrow Failure, and Infections
- Urinary Tract and Renal Toxicity
- Cardiotoxicity
- Pulmonary Toxicity
- Secondary Malignancies
- Veno-occlusive Liver Disease
- Alcohol Content
- Infertility
- Impaired Wound Healing
- Hyponatremia

### Clinical Trials and Postmarketing Experience

The following adverse reactions associated with the use of cyclophosphamide were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The most common adverse reactions were neutropenia, febrile neutropenia, fever, alopecia, nausea, vomiting, and diarrhea.

*Cardiac:* cardiac arrest, ventricular fibrillation, ventricular tachycardia, cardiogenic shock, pericardial effusion (progressing to cardiac tamponade), myocardial hemorrhage, myocardial infarction, cardiac failure (including fatal outcomes), cardiomyopathy, myocarditis, pericarditis, carditis, atrial fibrillation, supraventricular arrhythmia, ventricular arrhythmia, bradycardia, tachycardia, palpitations, QT prolongation.

# IMPORTANT SAFETY INFORMATION (CONTINUED)

*Congenital, Familial and Genetic:* intra-uterine death, fetal malformation, fetal growth retardation, fetal toxicity (including myelosuppression, gastroenteritis).

*Ear and Labyrinth:* deafness, hearing impaired, tinnitus.

*Endocrine:* water intoxication.

*Eye:* visual impairment, conjunctivitis, lacrimation.

*Gastrointestinal:* gastrointestinal hemorrhage, acute pancreatitis, colitis, enteritis, cecitis, stomatitis, constipation, parotid gland inflammation, nausea, vomiting, diarrhea.

*General Disorders and Administrative Site Conditions:* multiorgan failure, general physical deterioration, influenza-like illness, injection/infusion site reactions (thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema), pyrexia, edema, chest pain, mucosal inflammation, asthenia, pain, chills, fatigue, malaise, headache, febrile neutropenia.

*Hematologic:* myelosuppression, bone marrow failure, disseminated intravascular coagulation and hemolytic uremic syndrome (with thrombotic microangiopathy).

*Hepatic:* veno-occlusive liver disease, cholestatic hepatitis, cytolytic hepatitis, hepatitis, cholestasis; hepatotoxicity with hepatic failure, hepatic encephalopathy, ascites, hepatomegaly, blood bilirubin increased, hepatic function abnormal, hepatic enzymes increased.

*Immune:* immunosuppression, anaphylactic shock and hypersensitivity reaction.

*Infections:* The following manifestations have been associated with myelosuppression and immunosuppression caused by cyclophosphamide: increased risk for and severity of pneumonias (including fatal outcomes), other bacterial, fungal, viral, protozoal and, parasitic infections; reactivation of latent infections, (including viral hepatitis, tuberculosis), Pneumocystis jiroveci, herpes zoster, Strongyloides, sepsis and septic shock.

*Investigations:* blood lactate dehydrogenase increased, C-reactive protein increased.

*Metabolism and Nutrition:* hyponatremia, fluid retention, blood glucose increased, blood glucose decreased.

*Musculoskeletal and Connective Tissue:* rhabdomyolysis, scleroderma, muscle spasms, myalgia, arthralgia.

*Neoplasms:* acute leukemia, myelodysplastic syndrome, lymphoma, sarcomas, renal cell carcinoma, renal pelvis cancer, bladder cancer, ureteric cancer, thyroid cancer.

*Nervous System:* encephalopathy, convulsion, dizziness, neurotoxicity has been reported and manifested as reversible posterior leukoencephalopathy syndrome, myelopathy, peripheral neuropathy, polyneuropathy, neuralgia, dysesthesia, hypoesthesia, paresthesia, tremor, dysgeusia, hypogeusia, parosmia.

*Pregnancy:* premature labor.

*Psychiatric:* confusional state.

*Renal and Urinary:* renal failure, renal tubular disorder, renal impairment, nephropathy toxic, hemorrhagic cystitis, bladder necrosis, cystitis ulcerative, bladder contracture, hematuria, nephrogenic diabetes insipidus, atypical urinary bladder epithelial cells.

# IMPORTANT SAFETY INFORMATION (CONTINUED)

*Reproductive System:* infertility, ovarian failure, ovarian disorder, amenorrhea, oligomenorrhea, testicular atrophy, azoospermia, oligospermia.

*Respiratory:* pulmonary veno-occlusive disease, acute respiratory distress syndrome, interstitial lung disease as manifested by respiratory failure (including fatal outcomes), obliterative bronchiolitis, organizing pneumonia, alveolitis allergic, pneumonitis, pulmonary hemorrhage; respiratory distress, pulmonary hypertension, pulmonary edema, pleural effusion, bronchospasm, dyspnea, hypoxia, cough, nasal congestion, nasal discomfort, oropharyngeal pain, rhinorrhea.

*Skin and Subcutaneous Tissue:* toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pamar-plantar erythrodysesthesia syndrome, radiation recall dermatitis, toxic skin eruption, urticaria, dermatitis, blister, pruritus, erythema, nail disorder, facial swelling, hyperhidrosis, alopecia.

*Tumor lysis syndrome:* like other cytotoxic drugs, cyclophosphamide may induce tumor-lysis syndrome and hyperuricemia in patients with rapidly growing tumors.

*Vascular:* pulmonary embolism, venous thrombosis, vasculitis, peripheral ischemia, hypertension, hypotension, flushing, hot flush.

## DRUG INTERACTIONS

### Effect of Other Drugs on Cyclophosphamide Exposure

Protease inhibitors:
Cyclophosphamide is a pro-drug that is activated by cytochrome P450s.
Concomitant use of protease inhibitors may increase the concentration of cytotoxic metabolites. Use of protease inhibitor-based regimens was found to be associated with a higher incidence of infections and neutropenia in patients receiving cyclophosphamide, doxorubicin, and etoposide (CDE) than use of a Non-Nucleoside Reverse Transcriptase Inhibitor-based regimen.

### Drugs that Potentiate Cyclophosphamide Toxicities

Drugs or agents with similar toxicities to Cyclophosphamide Injection and can potentiate these effects are listed below.

Drugs that increase hematotoxicity and/or immunosuppression

- ACE inhibitors: ACE inhibitors can cause leukopenia.
- Natalizumab
- Paclitaxel: Increased hematotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion.
- Thiazide diuretics
- Zidovudine

Drugs that increase cardiotoxicity

- Anthracyclines
- Cytarabine
- Pentostatin
- Radiation therapy of the cardiac region
- Trastuzumab

# IMPORTANT SAFETY INFORMATION (CONTINUED)

Drugs that increase pulmonary toxicity
- Amiodarone
- G-CSF, GM-CSF (granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor)

Drugs that increase nephrotoxicity
- Amphotericin B
- Indomethacin: Acute water intoxication has been reported with concomitant use of indomethacin

Drugs that potentiate increase in other toxicities
- Azathioprine: Increased risk of hepatotoxicity (liver necrosis)
- Busulfan: Increased incidence of hepatic veno-occlusive disease and mucositis has been reported.
- Protease inhibitors: Increased incidence of mucositis

Drugs that increase the risk of hemorrhagic cystitis
- Radiation treatment: Increased risk of hemorrhagic cystitis may result from a combined effect of cyclophosphamide and past or concomitant radiation treatment.

## Effect of Cyclophosphamide on Other Drugs

Etanercept
A higher incidence of non-cutaneous malignant solid tumors in patients with Wegener's granulomatosis occurred with the addition of etanercept to cyclophosphamide treatment.

Metronidazole
Acute encephalopathy has been reported in a patient receiving cyclophosphamide and metronidazole. In an animal study, the combination of cyclophosphamide with metronidazole was associated with increased cyclophosphamide toxicity.

Tamoxifen
Concomitant use of tamoxifen and chemotherapy may increase the risk of thromboembolic complications.

Coumarins
Both increased and decreased warfarin effect have been reported in patients receiving warfarin and cyclophosphamide.

Cyclosporine
Lower serum concentrations of cyclosporine have been observed in patients receiving a combination of cyclophosphamide and cyclosporine than in patients receiving only cyclosporine. This interaction may result in an increased incidence of graft-versus-host disease.

Depolarizing Muscle Relaxants
If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, alert the anesthesiologist. Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity. Prolonged apnea may occur with concurrent depolarizing muscle relaxants (e.g., succinylcholine).

# IMPORTANT SAFETY INFORMATION (CONTINUED)

## USE IN SPECIFIC POPULATIONS

### Pregnancy

Risk Summary
Based on its mechanism of action and published reports of effects in pregnant patients or animals, Cyclophosphamide Injection can cause fetal harm when administered to a pregnant woman. Exposure to cyclophosphamide during pregnancy may cause fetal malformations, miscarriage, fetal growth retardation, and toxic effects in the newborn *[see Data below]*. Cyclophosphamide is teratogenic and embryo-fetal toxic in mice, rats, rabbits and monkeys *[see Data below]*. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

*Human Data*
Malformations of the skeleton, palate, limbs and eyes as well as miscarriage have been reported after exposure to cyclophosphamide in the first trimester. Fetal growth retardation and toxic effects manifesting in the newborn, including leukopenia, anemia, pancytopenia, severe bone marrow hypoplasia, and gastroenteritis have been reported after exposure to cyclophosphamide.

*Animal Data*
Administration of cyclophosphamide to pregnant mice, rats, rabbits and monkeys during the period of organogenesis at doses at or below the dose in patients based on body surface area resulted in various malformations, which included neural tube defects, limb and digit defects and other skeletal anomalies, cleft lip and palate, and reduced skeletal ossification.

### Lactation

Risk Summary
Cyclophosphamide is present in breast milk. Neutropenia, thrombocytopenia, low hemoglobin, and diarrhea have been reported in infants breast fed by women treated with cyclophosphamide. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with Cyclophosphamide Injection and for 1 week after the last dose.

### Females and Males of Reproductive Potential

Cyclophosphamide Injection can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to the initiation of Cyclophosphamide Injection.

Contraception
*Females*
Advise female patients of reproductive potential to use effective contraception during treatment with Cyclophosphamide Injection and for up to 1 year after completion of therapy.

*Males*
Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment with Cyclophosphamide Injection and for 4 months after completion of therapy.

# IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

*Males*

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

## Pediatric Use

The safety and effectiveness of Cyclophosphamide Injection have been established in pediatric patients and information on this use is discussed throughout the full Patient information.

The alcohol content of Cyclophosphamide Injection should be taken into account when given to pediatric patients.

Pre-pubescent girls treated with cyclophosphamide generally develop secondary sexual characteristics normally and have regular menses. Ovarian fibrosis with apparently complete loss of germ cells after prolonged cyclophosphamide treatment in late pre-pubescence has been reported. Girls treated with cyclophosphamide who have retained ovarian function after completing treatment are at increased risk of developing premature menopause.

Pre-pubescent boys treated with cyclophosphamide develop secondary sexual characteristics normally, but may have oligospermia or azoospermia and increased gonadotropin secretion. Some degree of testicular atrophy may occur. Cyclophosphamide-induced azoospermia is reversible in some patients, though the reversibility may not occur for several years after cessation of therapy.

## Geriatric Use

There is insufficient data from clinical studies of cyclophosphamide available for patients 65 years of age and older to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac functioning, and of concomitant disease or other drug therapy.

## 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. Monitor patients with severe renal impairment ($Cr_{Cl}$ =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 Injection administration and dialysis should be considered.

# IMPORTANT SAFETY INFORMATION (CONTINUED)

### Hepatic Impairment

Patients with severe hepatic impairment have reduced conversion of cyclophosphamide to the active 4-hydroxyl metabolite, potentially reducing efficacy.

The alcohol content of Cyclophosphamide Injection should be taken into account when given to patients with hepatic impairment.

## 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.

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.

**Please see the full Prescribing Information for safety information, and dosing guidelines.**
**To report SUSPECTED ADVERSE REACTIONS, contact Avyxa Pharma, LLC at 1-888-520-0954 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**