Cyclophosphamide: Drug information

(For additional information see "Cyclophosphamide: Patient drug information" and see "Cyclophosphamide: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: Canada

Procytox

Pharmacologic Category

Antineoplastic Agent, Alkylating Agent; Antineoplastic Agent, Alkylating Agent (Nitrogen Mustard); Antirheumatic, Miscellaneous; Immunosuppressant Agent

Dosing: Adult

Cyclophosphamide is associated with a moderate to high emetic potential (depending on dose, regimen, or administration route); antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Roila 2016).

Malignancy:

IV: 40 to 50 mg/kg in divided doses over 2 to 5 days **or** 10 to 15 mg/kg every 7 to 10 days **or** 3 to 5 mg/kg twice weekly

Oral: 1 to 5 mg/kg/day (initial and maintenance dosing)

Indication specific and/or off-label uses/dosing:

Acute lymphoblastic leukemia (off-label dosing): Multiple-agent regimens:

Hyper-CVAD regimen: IV: 300 mg/m^2 over 3 hours (with mesna) every 12 hours for 6 doses on days 1, 2, and 3 during odd-numbered cycles (cycles 1, 3, 5, 7) of an 8-cycle phase (Kantarjian 2004)

CALGB8811 regimen: IV:

Adults <60 years: Induction phase: 1,200 mg/m^2 on day 1 of a 4-week cycle; Early intensification phase: 1,000 mg/m^2 on day 1 of a 4-week cycle (repeat once); Late intensification phase: 1,000 mg/m^2 on day 29 of an 8-week cycle (Larson 1995)

Adults ≥60 years: Induction phase: 800 mg/m^2 on day 1 of a 4-week cycle; Early intensification phase: 1,000 mg/m^2 on day 1 of a 4-week cycle (repeat once); Late intensification phase: 1,000 mg/m^2 on day 29 of an 8-week cycle (Larson 1995)

Breast cancer (off-label dosing):

AC regimen: IV: 600 mg/m^2 on day 1 every 21 days (in combination with doxorubicin) for 4 cycles (Fisher 1990)

CEF regimen: Oral: 75 mg/m^2/day days 1 to 14 every 28 days (in combination with epirubicin and

fluorouracil) for 6 cycles (Levine 1998)

CMF regimen: Oral: 100 mg/m^2/day days 1 to 14 every 28 days (in combination with methotrexate and fluorouracil) for 6 cycles (Levine 1998) **or** IV: 600 mg/m^2 on day 1 every 21 days (in combination with methotrexate and fluorouracil); Goldhirsch 1998)

Chronic lymphocytic leukemia (off-label dosing): IV: R-FC regimen: 250 mg/m^2/day for 3 days every 28 days (in combination with rituximab and fludarabine) for 6 cycles (Robak 2010)

Ewing sarcoma (off-label use): IV: VAC/IE regimen: VAC: 1,200 mg/m^2 (plus mesna) on day 1 of a 21-day treatment cycle (in combination with vincristine and doxorubicin [then dactinomycin when maximum doxorubicin dose reached]), alternates with IE (ifosfamide and etoposide) for a total of 17 cycles (Grier 2003)

Gestational trophoblastic tumors, high-risk (off-label use): IV: EMA/CO regimen: 600 mg/m^2 on day 8 of 2-week treatment cycle (in combination with etoposide, methotrexate, dactinomycin, and vincristine), continue for at least 2 treatment cycles after a normal hCG level (Escobar 2003; Lurain 2006)

Granulomatosis with polyangiitis (GPA; Wegener granulomatosis) (off-label use; in combination with glucocorticoids):

Low-dose: Oral: 1.5 to 2 mg/kg/day (Jayne 2003; Stone 2010) or 2 mg/kg/day until remission, followed by 1.5 mg/kg/day for 3 additional months (de Groot 2009; Harper 2012)

Pulse: IV: 15 mg/kg (maximum dose: 1,200 mg) every 2 weeks for 3 doses, followed by maintenance pulses of either 15 mg/kg IV (maximum dose: 1,200 mg) every 3 weeks or 2.5 to 5 mg/kg/day orally on days 1, 2, and 3 every 3 weeks for 3 months after remission achieved (de Groot 2009; Harper 2012)

Hodgkin lymphoma (off-label dosing): IV:

BEACOPP regimen: 650 mg/m^2 on day 1 every 3 weeks (in combination with bleomycin, etoposide, doxorubicin, vincristine, procarbazine, and prednisone) for 8 cycles (Diehl 2003)

BEACOPP escalated regimen: 1,200 mg/m^2 on day 1 every 3 weeks (in combination with bleomycin, etoposide, doxorubicin, vincristine, procarbazine, and prednisone) for 8 cycles (Diehl 2003)

Multiple myeloma (off-label dosing): Oral: CyBorD regimen: 300 mg/m^2 on days 1, 8, 15, and 22 every 4 weeks (in combination with bortezomib and dexamethasone) for 4 cycles; may continue beyond 4 cycles (Khan 2012) **or** 500 mg/m^2 on days 1, 8, and 15 every 3 weeks (in combination with bortezomib and dexamethasone) for 8 cycles (Kumar 2012)

Non-Hodgkin lymphoma (off-label dosing): IV:

R-CHOP regimen: 750 mg/m^2 on day 1 every 3 weeks (in combination with rituximab, doxorubicin, vincristine, and prednisone) for 8 cycles (Coiffier 2002)

R-EPOCH (dose adjusted) regimen: 750 mg/m^2 on day 5 every 3 weeks (in combination with rituximab, etoposide, prednisone, vincristine, and doxorubicin) for 6 to 8 cycles (Garcia-Suarez 2007)

CODOX-M/IVAC (Burkitt lymphoma): Cycles 1 and 3 (CODOX-M): 800 mg/m^2 on day 1, followed by 200 mg/m^2 on days 2 to 5 (Magrath 1996) **or** 800 mg/m^2 on days 1 and 2 (Lacasce 2004), in

combination with vincristine, doxorubicin, and methotrexate; CODOX-M alternates with IVAC (etoposide, ifosfamide, and cytarabine) for a total of 4 cycles

Immune thrombocytopenia, refractory (off-label use; Provan 2010):

Oral: 1 to 2 mg/kg/day for at least 16 weeks

IV: 300 to 1,000 mg/m^2 for 1 to 3 doses every 2 to 4 weeks

Lupus nephritis (off-label use): IV: 500 mg once every 2 weeks for 6 doses or 500 to 1,000 mg/m^2 once every month for 6 doses (Hahn 2012) **or** 500 to 1,000 mg/m^2 every month for 6 months, then every 3 months for a total of at least 2.5 years (Austin 1986; Gourley 1996)

Ovarian germ cell tumors (malignant; off-label use): IV: 150 mg/m^2 on days 1 to 5 every 28 days (in combination with dactinomycin and vincristine) for at least 10 cycles (Slayton 1985)

Pericarditis, recurrent (off-label use):

Oral: 100 to 150 mg daily for 2 to 3 months (Marcolongo 1995). Based on very limited data (case report); additional data may be necessary to further define the role of cyclophosphamide in the treatment of this condition.

IV: 600 mg/m^2 once every month (Agard 2007). Based on very limited data (case report); additional data may be necessary to further define the role of cyclophosphamide in the treatment of this condition.

Pheochromocytoma, malignant (off-label use): IV: 750 mg/m^2 on day 1 every 3 or 4 weeks (in combination with dacarbazine and vincristine) (Huang 2008). Additional data may be necessary to further define the role of dacarbazine in this condition.

Small cell lung cancer (SCLC), refractory (off-label use): IV: 1,000 mg/m^2 (maximum: 2,000 mg) on day 1 every 3 weeks (in combination with doxorubicin and vincristine) until disease progression or unacceptable toxicity (von Pawel 1999)

Stem cell transplant conditioning (off-label use): IV:

Nonmyeloablative transplant (allogeneic): 750 mg/m^2/day for 3 days beginning 5 days prior to transplant (in combination with fludarabine) (Khouri 2008)

Myeloablative transplant:

100 mg/kg (based on IBW, unless actual weight <95% of IBW) as a single dose 2 days prior to transplant (in combination with total body irradiation and etoposide) (Thompson 2008)

50 mg/kg/day for 4 days beginning 5 days before transplant (with or without antithymocyte globulin [equine]) (Champlin 2007)

50 mg/kg/day for 4 days beginning 5 days prior to transplant (in combination with busulfan) (Cassileth 1993)

60 mg/kg/day for 2 days (in combination with busulfan and total body irradiation) (Anderson 1996)

1,800 mg/m^2/day for 4 days beginning 7 days prior to transplant (in combination with etoposide and carmustine) (Reece 1991)

Uveitis (off-label use):

Oral: 20 to 100 mg daily (Diaz-Llopis 2009) **or** 100 to 150 mg daily (Purjari 2010) **or** 1 to 3 mg/kg/day (Jabs 2000); adjust dose based on response or toxicity. May use IV dosing for more resistant cases (Diaz-Llopis 2009).

IV: 750 to 1,000 mg every 4 weeks (Diaz-Llopis 2009)

Dosing: Pediatric

(For additional information see "Cyclophosphamide: Pediatric drug information")

Cyclophosphamide is associated with a moderate to high emetic potential (depending on dose, regimen, or administration route); antiemetics are recommended to prevent nausea and vomiting (Dupuis 2011).

Malignancy:

IV: 40 to 50 mg/kg in divided doses over 2 to 5 days **or** 10 to 15 mg/kg every 7 to 10 days **or** 3 to 5 mg/kg twice weekly

Oral: 1 to 5 mg/kg/day (initial and maintenance dosing)

Nephrotic syndrome, corticosteroid refractory or intolerant, or corticosteroid sparing: Oral: Initial: 2 mg/kg once daily for 8 to 12 weeks (maximum cumulative dose: 168 mg/kg); treatment beyond 90 days may increase the potential for sterility in males; treatment beyond 1 course is not recommended (Lombel 2013)

Indication specific and/or off-label uses/dosing:

Ewing sarcoma (off-label use): IV: VAC/IE regimen: VAC: 1200 mg/m^2 (plus mesna) on day 1 of a 21-day treatment cycle (in combination with vincristine and doxorubicin [then dactinomycin when maximum doxorubicin dose reached]), alternates with IE (ifosfamide and etoposide) for a total of 17 cycles (Grier 2003)

Hodgkin lymphoma (off-label dosing): IV: BEACOPP escalated regimen: 1200 mg/m^2 on day 0 of a 21-day treatment cycle (in combination with bleomycin, etoposide, doxorubicin, vincristine, prednisone, and procarbazine) for 4 cycles (Kelly 2011)

Lupus nephritis (off-label use): IV: 500 to 1000 mg/m^2 every month for 6 months, then every 3 months for a total of 2.5 to 3 years (Austin 1986; Gourley 1996; Lehman 2000)

Ovarian germ cell tumors (malignant; off-label use): IV: 150 mg/m^2 on days 1 to 5 every 28 days (in combination with dactinomycin and vincristine) for at least 10 cycles (Slayton 1985)

Neuroblastoma (off-label dosing): IV: CE-CAdO regimen, courses 3 and 4: 300 mg/m^2 days 1 to 5 every 21 days for 2 cycles (Rubie 1998) **or** 10 mg/kg days 1 to 5 every 21 days for 2 cycles (Rubie 2001). **Note:** Decreased doses may be recommended for newborns or children <10 kg.

Stem cell transplant conditioning (off-label use): Myeloablative transplant: IV: 50 mg/kg/day for 4 days beginning 5 days before transplant (with or without antithymocyte globulin [equine]) (Champlin 2007)

Wilms tumor, relapsed (off-label use): Infants, Children, and Adolescents: IV (in combination with

vincristine, doxorubicin, mesna, etoposide, filgrastim, and radiation therapy) (Green 2007):

Pediatrics ≤30 kg: 14.7 mg/kg days 1 to 5 of weeks 3, 9, 15, and 21 and 14.7 mg/kg days 1 to 3 of weeks 6, 12, 18, and 24

Pediatrics >30 kg: 440 mg/m^2 days 1 to 5 of weeks 3, 9, 15, and 21 and 440 mg/m^2 days 1 to 3 of weeks 6, 12, 18, and 24

Dosing: Geriatric

Refer to adult dosing; adjust for renal clearance.

Dosing: Renal Impairment

There are no dosage adjustments provided in the manufacturer's labeling (use with caution; elevated levels of metabolites may occur).

The following adjustments have also been recommended:

Aronoff 2007: Children and Adults:

Cl_{cr} ≥10 mL/minute: No dosage adjustment required.

Cl_{cr} <10 mL/minute: Administer 75% of normal dose.

Hemodialysis: Moderately dialyzable (20% to 50%); administer 50% of normal dose; administer after hemodialysis

Continuous ambulatory peritoneal dialysis (CAPD): Administer 75% of normal dose.

Continuous renal replacement therapy (CRRT): Administer 100% of normal dose.

Janus 2010: Hemodialysis: Administer 75% of normal dose; administer after hemodialysis

Hematopoietic stem cell transplantation (Bodge 2014):

Moderate impairment: No dosage adjustment necessary.

Moderate to severe impairment: Consider dosage reduction.

Hemodialysis: Administer after hemodialysis. Cyclophosphamide is 20% to 50% dialyzed.

International Myeloma Working Group (IMWG) Recommendations: The International Myeloma Working Group (IMWG) recommendations suggest that cyclophosphamide may be administered without dosage adjustment in multiple myeloma patients with renal impairment, including those on dialysis. The IMWG recommends the use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (preferred) or the Modification of Diet in Renal Disease (MDRD) formula to evaluate renal function estimation in multiple myeloma patients with a stable serum creatinine (Dimopoulos 2016).

Dosing: Hepatic Impairment

The conversion between cyclophosphamide to the active metabolite may be reduced in patients with severe hepatic impairment, potentially reducing efficacy.

There are no dosage adjustments provided in the manufacturer's labeling.

The following adjustments have been recommended (Floyd 2006):

Serum bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: Administer 75% of dose.

Serum bilirubin >5 mg/dL: Avoid use.

Dosing: Obesity

*American Society of Clinical Oncology (ASCO) Guidelines for appropriate chemotherapy dosing in obese adults with cancer (**Note:** Excludes HSCT dosing):* Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs 2012).

American Society for Blood and Marrow Transplantation (ASBMT) practice guideline committee position statement on chemotherapy dosing in obesity (Bubalo 2014):

Cy200 (cyclophosphamide total dose of 200 mg/kg): Use the lesser of IBW or actual body weight (ABW).

Cy120 (cyclophosphamide total dose of 120 mg/kg): Use either IBW or ABW for patients ≤120% IBW (preferred method for adults of all body sizes); use ABW25 for patients >120% IBW (preferred for pediatric patients).

ABW25: Adjusted wt (kg) = Ideal body weight (kg) + 0.25 [actual wt (kg) - ideal body weight (kg)]

Dosing: Adjustment for Toxicity

Hematologic toxicity: May require dose reduction or treatment interruption

Hemorrhagic cystitis, severe: Discontinue treatment.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, Oral:

Generic: 25 mg, 50 mg

Solution Reconstituted, Injection:

Generic: 500 mg (1 ea); 1 g (1 ea); 2 g (1 ea)

Tablet, Oral:

Generic: 25 mg [DSC], 50 mg [DSC]

Generic Equivalent Available (US) Yes

Dosage Forms: Canada Information with regard to form, strength, and availability of products uniquely available in Canada but currently not available in the US. Refer also to Dosage forms.

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 200 mg

Administration

Cyclophosphamide is associated with a moderate to high emetic potential (depending on dose, regimen, or administration route); antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Dupuis 2011; Roila 2016).

IV: Infusion rate may vary based on protocol (refer to specific protocol for infusion rate). Administer by direct IV injection (if reconstituted in NS), IVPB, or continuous IV infusion

Bladder toxicity: To minimize bladder toxicity, increase normal fluid intake during and for 1 to 2 days after cyclophosphamide dose. Most adult patients will require a fluid intake of at least 2 L/day. High-dose regimens should be accompanied by vigorous hydration with or without mesna therapy. Morning administration may be preferred to ensure adequate hydration throughout the day.

Hematopoietic stem cell transplant: Approaches to reduction of hemorrhagic cystitis include infusion of 0.9% NaCl 3 L/m^2/24 hours, infusion of 0.9% NaCl 3 L/m^2/24 hours with continuous 0.9% NaCl bladder irrigation 300 to 1000 mL/hour, and infusion of 0.9% NaCl 1.5 to 3 L/m^2/24 hours with intravenous mesna. Hydration should begin at least 4 hours before cyclophosphamide and continue at least 24 hours after completion of cyclophosphamide. The daily mesna dose (as a percentage of cyclophosphamide dose) may vary; refer to protocol and/or primary literature for mesna dose. Mesna can be administered as a continuous 24-hour intravenous infusion or be given in divided doses every 4 hours. Mesna should begin at the start of treatment, and continue at least 24 hours following the last dose of cyclophosphamide.

Oral: Tablets are not scored and should not be cut, chewed, or crushed. Swallow capsules whole; do not open, crush, or chew. To minimize bladder toxicity, increase normal fluid intake. Morning administration may be preferred to ensure adequate hydration throughout the day; do not administer tablets/capsules at bedtime. Avoid exposure to broken capsules; if contact occurs, wash hands immediately and thoroughly.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends single gloving for administration of intact tablets or capsules. If manipulating tablets/capsules (eg, to prepare an oral suspension), NIOSH recommends double gloving, a protective gown, and preparation in a controlled device; if not prepared in a controlled device, respiratory and eye/face protection as well as ventilated engineering controls are recommended. NIOSH recommends double gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid/feeding tube administration. For IV preparation, NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs). Double gloving, a gown, and (if dosage

form allows) CSTDs are required during IV administration (NIOSH 2016).

Use

Oncology uses: Treatment of acute lymphoblastic leukemia (ALL), acute myelocytic leukemia (AML), breast cancer, chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), Hodgkin lymphoma, mycosis fungoides, multiple myeloma, neuroblastoma, non-Hodgkin lymphomas (including Burkitt lymphoma), ovarian adenocarcinoma, and retinoblastoma

Limitations of use: Although potentially effective as a single-agent in susceptible malignancies, cyclophosphamide is more frequently used in combination with other chemotherapy drugs

Nononcology uses: Nephrotic syndrome: Treatment of minimal change nephrotic syndrome (biopsy proven) in children who are unresponsive or intolerant to corticosteroid therapy

Limitations of use: The safety and efficacy for the treatment of nephrotic syndrome in adults or in other renal diseases has not been established.

Use: Off-Label

Ewing sarcoma; Gestational trophoblastic tumors, high-risk; Granulomatosis with polyangiitis (GPA; Wegener granulomatosis); Hematopoietic stem cell transplant conditioning; Immune thrombocytopenia, refractory (adults); Lupus nephritis; Ovarian germ cell tumors (malignant); Pericarditis (recurrent); Pheochromocytoma (malignant); Small cell lung cancer (refractory); Uveitis (adults); Wilms tumor (relapsed); Antibody-induced pure red cell aplasia; Autoimmune hemolytic anemia; Juvenile idiopathic arthritis (refractory); Myasthenia gravis; Rhabdomyosarcoma; Rheumatoid disorders (severe); Waldenström macroglobulinemia

Medication Safety Issues

Sound-alike/look-alike issues:

Cyclophosphamide may be confused with cycloSPORINE, ifosfamide

Cytoxan may be confused with cefOXitin, Ciloxan, cytarabine, CytoGam, Cytosar, Cytosar-U, Cytotec

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Geriatric Patients: High-Risk Medication:

Beers Criteria: Cyclophosphamide is identified in the Beers Criteria as a potentially inappropriate medication to be used with caution in patients 65 years and older due to the potential to cause or exacerbate syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatremia; monitor sodium concentration closely when initiating or adjusting the dose in older adults (Beers Criteria [AGS 2015]).

Adverse Reactions Frequency not defined.

Dermatologic: Alopecia (reversible; onset: 3 to 6 weeks after start of treatment)

Endocrine & metabolic: Altered hormone level (increased gonadotropin secretion), amenorrhea

Gastrointestinal: Abdominal pain, anorexia, diarrhea, mucositis, nausea and vomiting (dose-related), stomatitis

Genitourinary: Azoospermia, defective oogenesis, hemorrhagic cystitis, oligospermia, sterility

Hematologic & oncologic: Anemia, bone marrow depression, febrile neutropenia, leukopenia (dose-related; recovery: 7 to 10 days after cessation), neutropenia, thrombocytopenia

Infection: Infection

<1%, postmarketing, and/or case reports: Acute respiratory distress, anaphylaxis, auditory disturbance, blurred vision, cardiac arrhythmia (with high-dose [HSCT] therapy), cardiac failure (with high-dose [HSCT] therapy), cardiac tamponade (with high-dose [HSCT] therapy), cardiotoxicity, confusion, C-reactive protein increased, dizziness, dyschromia (skin/fingernails), dyspnea, erythema multiforme, gastrointestinal hemorrhage, heart block, hematuria, hemopericardium, hemorrhagic colitis, hemorrhagic myocarditis (with high-dose [HSCT] therapy), hemorrhagic ureteritis, hepatic veno-occlusive disease, hepatitis, hepatotoxicity, hypersensitivity reaction, hyperuricemia, hypokalemia, hyponatremia, increased lactate dehydrogenase, interstitial pneumonitis, jaundice, malaise, mesenteric ischemia (acute), metastases, methemoglobinemia (with high-dose [HSCT] therapy), multi-organ failure, myocardial necrosis (with high-dose [HSCT] therapy), neurotoxicity, neutrophilic eccrine hidradenitis, ovarian fibrosis, pancreatitis, pericarditis, pneumonia, pulmonary hypertension, pulmonary infiltrates, pulmonary interstitial fibrosis (with high doses), pulmonary veno-occlusive disease, pyelonephritis, radiation recall phenomenon, reactivation of disease, reduced ejection fraction, renal tubular necrosis, reversible posterior leukoencephalopathy syndrome, rhabdomyolysis, sepsis, septic shock, SIADH, skin rash, Stevens-Johnson syndrome, testicular atrophy, thrombocytopenia (immune-mediated), thrombosis (arterial and venous), toxic epidermal necrolysis, toxic megacolon, tumor lysis syndrome, urinary fibrosis, weakness, wound healing impairment

Contraindications

US labeling: Hypersensitivity to cyclophosphamide or any component of the formulation; urinary outflow obstruction

Canadian labeling: Hypersensitivity to cyclophosphamide or its metabolites, urinary outflow obstructions, severe myelosuppression, severe renal or hepatic impairment, active infection (especially varicella zoster), severe immunosuppression

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: Leukopenia, neutropenia, thrombocytopenia, and anemia may commonly occur; may be dose related. Bone marrow failure has been reported. Bone marrow failure and severe immunosuppression may lead to serious (and fatal) infections, including sepsis and septic shock, or may reactive latent infections. Antimicrobial prophylaxis may be considered in

appropriate patients. Initiate antibiotics for neutropenic fever; antifungal and antiviral medications may also be necessary. Monitor blood counts during treatment. Avoid use if neutrophils are ≤1,500/mm^3 and platelets are <50,000/mm^3. Consider growth factors (primary or secondary prophylaxis) in patients at increased risk for complications due to neutropenia. Platelet and neutrophil nadirs are usually at weeks 1 and 2 of treatment and recovery is expected after ~20 days. Severe myelosuppression may be more prevalent in heavily pretreated patients or in patients receiving concomitant chemotherapy and/or radiation therapy.

• Cardiotoxicity: Cardiotoxicity has been reported (some fatal), usually with high doses associated with transplant conditioning regimens, although may rarely occur with lower doses. Cardiac abnormalities do not appear to persist. Cardiotoxicities reported have included arrhythmias (supraventricular and ventricular [some with QT prolongation]), congestive heart failure, heart block, hemopericardium (secondary to hemorrhagic myocarditis and myocardial necrosis), myocarditis (including hemorrhagic), pericarditis, pericardial effusion including cardiac tamponade, and tachyarrhythmias. Cardiotoxicity is related to endothelial capillary damage; symptoms may be managed with diuretics, ACE inhibitors, beta-blockers, or inotropics (Floyd 2005). The risk for cardiotoxicity may be increased with higher doses, advanced age, prior radiation to the cardiac region, and in patients who have received prior or concurrent cardiotoxic medication. Use with caution in patients with preexisting cardiovascular disease or those at risk for cardiotoxicity. For patients with cardiac risk factors or preexisting cardiac disease, monitor during treatment. In a scientific statement from the American Heart Association, cyclophosphamide has been determined to be an agent that may either cause reversible direct myocardial toxicity or exacerbate underlying myocardial dysfunction (magnitude: moderate/major) (AHA [Page 2016]).

• Fertility effects: May impair fertility; interferes with oogenesis and spermatogenesis. Effect on fertility is generally dependent on dose and duration of treatment and may be irreversible. The age at treatment initiation and cumulative dose were determined to be risk factors for ovarian failure in cyclophosphamide use for the treatment of systemic lupus erythematosus (SLE) (Mok 1998).

• Gastrointestinal adverse effects: Nausea and vomiting commonly occur. Cyclophosphamide is associated with a moderate to high emetic potential (depending on dose, regimen, or administration route); antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Dupuis 2011; Roila 2016). Stomatitis/mucositis may also occur.

• Hepatotoxicity: Hepatic sinusoidal obstruction syndrome (SOS), formerly called veno-occlusive liver disease (VOD), has been reported in patients receiving chemotherapy regimens containing cyclophosphamide. A major risk factor for SOS is cytoreductive conditioning transplantation regimens with cyclophosphamide used in combination with total body irradiation or busulfan (or other agents). Other risk factors include preexisting hepatic dysfunction, prior radiation to the abdominal area, and low performance status. Children <3 years of age are reported to be at increased risk for hepatic SOS; monitor for signs or symptoms of hepatic SOS, including bilirubin >1.4 mg/dL, unexplained weight gain, ascites, hepatomegaly, or unexplained right upper quadrant pain (Arndt 2004). SOS has also been reported in patients receiving long-term lower doses for immunosuppressive indications.

• Hypersensitivity: Anaphylactic reactions have been reported. Cross-sensitivity with other alkylating agents may occur.

• Hyponatremia: Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome resembling SIADH (syndrome of inappropriate secretion of antidiuretic hormone)

has been reported; some have been fatal.

• Immunosuppression: Monitor for infections; immunosuppression and serious infections may occur. Serious infections may require dose reduction, or interruption or discontinuation of treatment.

• Pulmonary toxicities: Pulmonary toxicities, including pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease, and acute respiratory distress syndrome, have been reported. Monitor for signs/symptoms of pulmonary toxicity. Consider pulmonary function testing to assess the severity of pneumonitis (Morgan 2011). Cyclophosphamide-induced pneumonitis is rare and may present as early (within 1 to 6 months) or late onset (several months to years). Early onset may be reversible with discontinuation; late onset is associated with pleural thickening and may persist chronically (Malik 1996). In addition, late onset pneumonitis (>6 months after therapy initiation) may be associated with increased mortality.

• Secondary malignancies: Secondary malignancies (bladder cancer, myelodysplasia, acute leukemias, lymphomas, thyroid cancer, and sarcomas) have been reported with both single-agent and with combination chemotherapy regimens; onset may be delayed (up to several years after treatment). Bladder cancer usually occurs in patients previously experiencing hemorrhagic cystitis; risk may be reduced by preventing hemorrhagic cystitis.

• Urinary/renal toxicity: Cyclophosphamide is associated with the development of hemorrhagic cystitis, pyelitis, ureteritis, and hematuria. Hemorrhagic cystitis may rarely be severe or fatal. Bladder fibrosis may also occur, either with or without cystitis. Urotoxicity is due to excretion of cyclophosphamide metabolites in the urine and appears to be dose- and treatment duration-dependent, although may occur with short-term use. Increased hydration and frequent voiding is recommended to help prevent cystitis; some protocols utilize mesna to protect against hemorrhagic cystitis. Monitor urinalysis for hematuria or other signs of urotoxicity. Severe or prolonged hemorrhagic cystitis may require medical or surgical treatment. While hematuria generally resolves within a few days after treatment is withheld, it may persist in some cases. Discontinue cyclophosphamide with severe hemorrhagic cystitis. Exclude or correct any urinary tract obstructions prior to treatment initiation (use is contraindicated with bladder outlet obstruction). Use with caution (if at all) in patients with active urinary tract infection.

• Wound healing impairment: May interfere with wound healing.

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment may be needed. The conversion between cyclophosphamide to the active metabolite may be reduced in patients with severe hepatic impairment, potentially reducing efficacy.

• Renal impairment: Use with caution in patients with renal impairment; dosage adjustment may be needed. Decreased renal excretion and increased serum levels (cyclophosphamide and metabolites) may occur in patients with severe renal impairment (CrCl 10 to 24 mL/minute); monitor for signs/symptoms of toxicity. Cyclophosphamide and metabolites are dialyzable; differences in amount dialyzed may occur due to dialysis system used. If dialysis is required, maintain a consistent interval between administration and dialysis.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions

database for more detailed information. Cyclophosphamide may potentiate the cardiotoxicity of anthracyclines.

Metabolism/Transport Effects

Substrate of CYP2A6 (minor), CYP2B6 (major), CYP2C19 (minor), CYP2C9 (minor), CYP3A4 (minor); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Induces** CYP2C9 (weak/moderate)

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Allopurinol: May enhance the adverse/toxic effect of Cyclophosphamide. Specifically, bone marrow suppression. *Risk C: Monitor therapy*

Amiodarone: Cyclophosphamide may enhance the adverse/toxic effect of Amiodarone. Specifically, the risk of pulmonary toxicity may be enhanced. *Risk C: Monitor therapy*

Antineoplastic Agents (Anthracycline, Systemic): Cyclophosphamide may enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline, Systemic). *Risk C: Monitor therapy*

AzaTHIOprine: May enhance the hepatotoxic effect of Cyclophosphamide. *Risk C: Monitor therapy*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Belimumab: May enhance the adverse/toxic effect of Cyclophosphamide. *Risk X: Avoid combination*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

CycloSPORINE (Systemic): Cyclophosphamide may enhance the immunosuppressive effect of CycloSPORINE (Systemic). Cyclophosphamide may decrease the serum concentration of CycloSPORINE (Systemic). *Risk C: Monitor therapy*

CYP2B6 Inducers (Moderate): May decrease the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

Dabrafenib: May decrease the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Etanercept: May enhance the adverse/toxic effect of Cyclophosphamide. An increased risk of solid cancer development may be present. *Risk X: Avoid combination*

Filgrastim: May enhance the adverse/toxic effect of Cyclophosphamide. Specifically, the risk of pulmonary toxicity may be enhanced. *Risk C: Monitor therapy*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: May enhance the adverse/toxic effect of Cyclophosphamide. Specifically, the risk of pulmonary toxicity may be enhanced. Cyclophosphamide may diminish the therapeutic effect of Lenograstim. Management: Avoid the use of lenograstim 24 hours before until 24 hours after the completion of bleomycin infusion. Monitor for enhanced pulmonary toxicity when cyclophosphamide and lenograstim are given in combination. *Risk D: Consider therapy modification*

Lumacaftor: May decrease the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

MiFEPRIStone: May increase the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nilotinib: May decrease the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

Pentostatin: May enhance the cardiotoxic effect of Cyclophosphamide. *Risk C: Monitor therapy*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Protease Inhibitors: May enhance the adverse/toxic effect of Cyclophosphamide. Specifically, the

incidences of neutropenia, infection, and mucositis may be increased. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sargramostim: Cyclophosphamide may enhance the adverse/toxic effect of Sargramostim. Specifically, the risk of pulmonary toxicity may be enhanced. *Risk C: Monitor therapy*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

Succinylcholine: Cyclophosphamide may increase the serum concentration of Succinylcholine. Management: Consider alternatives to succinylcholine in patients who have received cyclophosphamide in the past 10 days, or reduced succinylcholine doses (a serum pseudocholinesterase assay may help inform this reduction) with close monitoring. *Risk D: Consider therapy modification*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Thiazide and Thiazide-Like Diuretics: May enhance the adverse/toxic effect of Cyclophosphamide. Specifically, granulocytopenia may be enhanced. *Risk C: Monitor therapy*

Thiotepa: May increase the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Pregnancy Risk Factor

D (show table)

Pregnancy Implications

Cyclophosphamide crosses the placenta and can be detected in amniotic fluid (D'Incalci 1982). Based on the mechanism of action, cyclophosphamide may cause fetal harm if administered during pregnancy. Adverse events (including ectrodactylia) were observed in human studies following exposure to cyclophosphamide. Women of childbearing potential should avoid pregnancy while receiving cyclophosphamide and for up to 1 year after completion of treatment. Males with female partners

who are or may become pregnant should use a condom during and for at least 4 months after cyclophosphamide treatment. Cyclophosphamide may cause sterility in males and females (may be irreversible) and amenorrhea in females. When treatment is needed for lupus nephritis, cyclophosphamide should be avoided in women who are pregnant or those who wish to preserve their fertility (Hahn 2012).

Chemotherapy, if indicated, may be administered to pregnant women with breast cancer as part of a combination chemotherapy regimen (common regimens administered during pregnancy include doxorubicin (or epirubicin), cyclophosphamide, and fluorouracil); chemotherapy should not be administered during the first trimester, after 35 weeks gestation, or within 3 weeks of planned delivery (Amant 2010; Loibl 2006). The European Society for Medical Oncology has published guidelines for diagnosis, treatment, and follow-up of cancer during pregnancy. The guidelines recommend referral to a facility with expertise in cancer during pregnancy and encourage a multidisciplinary team (obstetrician, neonatologist, oncology team). In general, if chemotherapy is indicated, it should be avoided during in the first trimester, there should be a 3-week time period between the last chemotherapy dose and anticipated delivery, and chemotherapy should not be administered beyond week 33 of gestation (Peccatori 2013).

Breast-Feeding Considerations Cyclophosphamide is excreted into breast milk. Leukopenia and thrombocytopenia were noted in an infant exposed to cyclophosphamide while nursing. The mother was treated with one course of cyclophosphamide 6 weeks prior to delivery then cyclophosphamide IV 6 mg/kg (300 mg) once daily for 3 days beginning 20 days postpartum. Complete blood counts were obtained in the breast-feeding infant on each day of therapy; WBC and platelets decreased by day 3 (Durodola 1979). Due to the potential for serious adverse effects in the nursing infant, a decision should be made to discontinue cyclophosphamide or to discontinue breast-feeding, taking into account the importance of treatment to the mother.

Monitoring Parameters CBC with differential and platelets, BUN, UA, serum electrolytes, serum creatinine; monitor for signs/symptoms of hemorrhagic cystitis or other urinary/renal toxicity, pulmonary, cardiac, and/or hepatic toxicity

Mechanism of Action Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is a cell cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunosuppressive activity. Cyclophosphamide is a prodrug that must be metabolized to active metabolites in the liver.

Pharmacodynamics/Kinetics

Absorption: Oral: Well absorbed

Distribution: V_d: 30 to 50 L (approximates total body water); crosses into CSF (not in high enough concentrations to treat meningeal leukemia)

Protein binding: ~20%; some metabolites are bound at >60%

Metabolism: Hepatic to active metabolites acrolein, 4-aldophosphamide, 4-hydroperoxycyclophosphamide, and nor-nitrogen mustard

Bioavailability: >75%

Half-life elimination: IV: 3 to 12 hours; Children: 4 hours; Adults: 6 to 8 hours

Time to peak: Oral: ~1 hour; IV: Metabolites: 2 to 3 hours

Excretion: Urine (10 to 20% as unchanged drug); feces (4%)

Pricing: US

Capsules (Cyclophosphamide Oral)

25 mg (100): $936.20

50 mg (100): $1718.11

Solution (reconstituted) (Cyclophosphamide Injection)

1 g (1): $685.61

2 g (1): $1371.22

500 mg (1): $343.44

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Alkyloxan (KR, SG); Alkyroxan (KR); Cryofaxol (CR, DO, GT, HN, MX, NI, PA, SV); Cycloblastin (AU, NZ); Cycloblastine (LU); Cyclostin (DE); Cyclostin N (DE); Cycram (VN); Cyphos (LK, PH); Cytoxan (CO, HU, ID); Endoksan (UA); Endoxan (AT, AU, BE, BG, CL, CZ, DE, EE, EG, GR, HN, HR, HU, IL, IT, KR, LT, LU, LV, NL, NZ, PK, PL, PT, RO, RU, SG, SI, SK, TR, UY, VN, ZA); Endoxan-Asta (AE, AR, BH, CH, CY, FR, HK, ID, IN, IQ, IR, JO, KW, LB, LY, MY, OM, PH, QA, SA, SY, TH, TW, YE); Endoxana (GB); Endoxon-Asta (AU); Enduxan (BR); Formitex (CR, DO, GT, HN, NI, PA, SV); Genoxal (BR, ES); Hidrofosmin (CR, DO, GT, HN, NI, PA, SV); Ledoxan (PH); Ledoxina (MX); Lyophilisate (ID); Neophamid (KR); Neophos (LB); Oncomide (LK); Sendoxan (DK, FI, NO, SE); Syklofosfamid (TR, TW); Xyclomed (PH)

REFERENCES

1. *Agard C, Rendu E, Leguern V, et al. Churg-Strauss syndrome revealed by granulomatous acute pericarditis: two case reports and a review of the literature. Semin Arthritis Rheum. 2007;36(6):386-391. [PubMed 17303217]*
2. *Amant F, Deckers S, Van Calsteren K, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. Eur J Cancer. 2010;46(18):3158-3168. [PubMed 20932740]*
3. *American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227-2246. doi:10.1111/jgs.13702. [PubMed 26446832]*
4. *Anderson JE, Appelbaum FR, Schoch G, et al, "Allogeneic Marrow Transplantation for Myelodysplastic Syndrome With Advanced Disease Morphology: A Phase II Study of Busulfan, Cyclophosphamide, and Total Body-Irradiation and Analysis of Prognostic Factors," J Clin Oncol, 1996, 14(1):220-6. [PubMed 8558201]*
5. *Arndt C, Hawkins, D, Anderson JR, et al. Age is a Risk Factor for Chemotherapy-Induced Hepatopathy With Vincristine, Dactinomycin and Cyclophosphamide. J Clin Oncol. 2004;22(10):1894-1901. [PubMed 15143082]*
6. *Aronoff GR, Bennett WM, Berns JS, et al, Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children, 5th ed. Philadelphia, PA: American College of Physicians; 2007, p 97, 170.*

7. *Austin HA 3rd, Klipel JH, Balow JE, et al, “Therapy of Lupus Nephritis. Controlled Trial of Prednisone and Cytotoxic Drugs,” N Engl J Med, 1986, 314(10):614-9. [PubMed 3511372]*
8. *Basch E, Prestrud AA, Hesketh PJ, et al, "Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update," J Clin Oncol, 2011, 29(31):4189-98. [PubMed 21947834]*
9. *Beukelman T, Patkar NM, Saag KG, et al, “2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features,” Arthritis Care Res (Hoboken), 2011, 63(4):465-82. [PubMed 21452260]*
10. *Bodge MN, Reddy S, Thompson MS, Savani BN. Preparative regimen dosing for hematopoietic stem cell transplantation in patients with chronic kidney disease: analysis of the literature and recommendations. Biol Blood Marrow Transplant. 2014;20(7):908-919. [PubMed 24565993]10.1016/j.bbmt.2014.02.013*
11. *Bonadonna G, Valagussa P, Moliterni A, et al, “Adjuvant Cyclophosphamide, Methotrexate, and Fluorouracil in Node-Positive Breast Cancer: The Results of 20 Years of Follow-Up,” N Engl J Med, 1995, 332(14):901-6. [PubMed 7877646]*
12. *Bubalo J, Carpenter PA, Majhail N, et al. Conditioning chemotherapy dose adjustment in obese patients: a review and position statement by the American Society for Blood and Marrow Transplantation practice guideline committee. Biol Blood Marrow Transplant. 2014;20(5):600-616. [PubMed 24462742]*
13. *Cassileth PA, Andersen J, Lazarus HM, et al, “Autologous Bone Marrow Transplant in Acute Myeloid Leukemia in First Remission,” J Clin Oncol, 1993, 11(2):314-9. [PubMed 8426209]*
14. *Champlin RE, Perez WS, Passweg JR, et al, “Bone Marrow Transplantation for Severe Aplastic Anemia: A Randomized Controlled Study of Conditioning Regimens,” Blood, 2007, 109(10):4582-5. [PubMed 17272503]*
15. *Chang C, Storer BE, Scott BL, et al, “Hematopoietic Cell Transplantation in Patients With Myelodysplastic Syndrome or Acute Myeloid Leukemia Arising From Myelodysplastic Syndrome: Similar Outcomes in Patients With De Novo Disease and Disease Following Prior Therapy or Antecedent Hematologic Disorders,” Blood, 2007, 110(4):1379-87. [PubMed 17488876]*
16. *Coiffier B, Lepage E, Briere J, et al, “CHOP Chemotherapy Plus Rituximab Compared With CHOP Alone in Elderly Patients With Diffuse Large-B-Cell Lymphoma,” N Engl J Med, 2002, 346(4):235-42. [PubMed 11807147]*
17. *Cyclophosphamide Capsules [prescribing information]. Columbus, OH: Roxane; September 2013.*
18. *Cyclophosphamide Injection [prescribing information]. Deerfield, IL: Baxter; June 2015.*
19. *Cyclophosphamide Injection and Tablets [prescribing information]. Deerfield, IL: Baxter; November 2013.*
20. *Cyclophosphamide Injection and Tablets [prescribing information]. Deerfield, IL: Baxter; May 2013.*
21. *Deeg HJ, Shulman HM, Anderson JE, et al, “Allogeneic and Syngeneic Marrow Transplantation for Myelodysplastic Syndrome in Patients 55 to 66 Years of Age,” Blood, 2000, 95 (4):1188-94. [PubMed 10666189]*
22. *de Groot K, Harper L, Jayne DR, et al, “Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Randomized Trial,” Ann Intern Med, 2009, 150(10):670-80. [PubMed 19451574]*
23. *de Jonge ME, Huitema AD, van Dam SM, et al, “Significant Induction of Cyclophosphamide and Thiotepa Metabolism by Phenytoin,” Cancer Chemother Pharmacol, 2005, 55(5):507-10. [PubMed 15685452]*
24. *DeLeve LD, Shulman HM, and McDonald GB, "Toxic Injury to Hepatic Sinusoids: Sinusoidal Obstruction Syndrome (Veno-Occlusive Disease)," Semin Liver Dis, 2002, F22(1):27-42. [PubMed 11928077]*
25. *Díaz-Llopis M, Gallego-Pinazo R, García-Delpech S, et al. General principles for the treatment of non-infectious uveitis. Inflamm Allergy Drug Targets. 2009;8(4):260-265. [PubMed 19754409]*
26. *Diehl V, Franklin J, Pfreundschuh M, et al, "Standard and Increased-Dose BEACOPP Chemotherapy Compared With COPP-ABVD for Advanced Hodgkin's disease," N Engl J Med, 2003, 348(24):2386-95. [PubMed 12802024]*
27. *Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol. 2016;34(13):1544-1557. [PubMed 26976420]10.1200/JCO.2015.65.0044*
28. *D'Incalci M, Sessa C, Colombo N, et al. Transplacental passage of cyclophosphamide. Cancer Treat Rep. 1982;66(8):1681-1682. [PubMed 7105061]*
29. *Dupuis LL, Boodhan S, Holdsworth M, et al; Pediatric Oncology Group of Ontario. Guideline for the prevention of acute*

nausea and vomiting due to antineoplastic medication in pediatric cancer patients. Pediatr Blood Cancer. 2013;60(7):1073-1082. [PubMed 23512831]

30. *Dupuis LL, Boodhan S, Sung L, "Guideline for the Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients," Pediatr Blood Cancer, 2011, 57(2):191-8. [PubMed 21465637]*
31. *Durodola JI. Administration of cyclophosphamide during late pregnancy and early lactation: a case report. J Natl Med Assoc. 1979;71(2):165-166. [PubMed 423292]*
32. *Durrani K, Papaliodis GN, Foster CS. Pulse IV cyclophosphamide in ocular inflammatory disease: efficacy and short-term safety. Ophthalmology. 2004;111(5):960-965. [PubMed 15121375]*
33. *Eder JP, Elias A, Shea TC, et al, "A Phase I-II Study of Cyclophosphamide, Thiotepa, and Carboplatin With Autologous Bone Marrow Transplantation in Solid Tumor Patients," J Clin Oncol, 1990, 8(7):1239-45. [PubMed 2162912]*
34. *Escobar PF, Lurain JR, Singh DK, et al, "Treatment of High-Risk Gestational Trophoblastic Neoplasia With Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, and Vincristine Chemotherapy," Gynecol Oncol, 2003, 91(3):552-7. [PubMed 14675675]*
35. *Fisher B, Brown AM, Dimitrov NV, et al, "Two Months of Doxorubicin-Cyclophosphamide With and Without Interval Reinduction Therapy Compared With 6 Months of Cyclophosphamide, Methotrexate, and Fluorouracil in Positive-Node Breast Cancer Patients With Tamoxifen-Nonresponsive Tumors: Results From the National Surgical Adjuvant Breast and Bowel Project B-15," J Clin Oncol, 1990, 8(9):1483-96. [PubMed 2202791]*
36. *Floyd J, Mirza I, Sachs B, et al, "Hepatotoxicity of Chemotherapy," Semin Oncol, 2006, 33(1):50-67. [PubMed 16473644]*
37. *Floyd JD, Nguyen DT, Lobins RL, et al, "Cardiotoxicity of Cancer Therapy," J Clin Oncol, 2005, 23(30):7685-96. [PubMed 16234530]*
38. *Fraiser LH, Kanekal S, and Kehrer JP, "Cyclophosphamide Toxicity. Characterizing and Avoiding the Problem," Drugs, 1991, 42(5):781-95. [PubMed 1723374]*
39. *García-Suárez J, Bañas H, Arribas I, et al, "Dose-Adjusted EPOCH Plus Rituximab is an Effective Regimen in Patients With Poor-Prognostic Untreated Diffuse Large B-Cell Lymphoma: Results From a Prospective Observational Study," Br J Haematol, 2007, 136(2):276-85. [PubMed 17233819]*
40. *Giralt SA, LeMaistre CF, Vriesendorp HM, et al, "Etoposide, Cyclophosphamide, Total-Body Irradiation and Allogeneic Bone Marrow Transplantation for Hematologic Malignancies," J Clin Oncol, 1994, 12(9):1923-30. [PubMed 8083714]*
41. *Glynn SA, Boersma BJ, Howe TM, et al, "A Mitochondrial Target Sequence Polymorphism in Manganese Superoxide Dismutase Predicts Inferior Survival in Breast Cancer Patients Treated With Cyclophosphamide," Clin Cancer Res, 2009, 15(12):4165-73. [PubMed 19509150]*
42. *Goldhirsch A, Colleoni M, Coates AS, et al, "Adding Adjuvant CMF Chemotherapy to Either Radiotherapy or Tamoxifen: Are All CMFs Alike? The International Breast Cancer Study Group (IBCSG)," Ann Oncol, 1998, 9(5):489-93. [PubMed 9653488]*
43. *Gourley MF, Austin HA 3rd, Scott D, et al, "Methylprednisolone and Cyclophosphamide, Alone or in Combination, in Patients With Lupus Nephritis. A Randomized, Controlled Trial," Ann Intern Med, 1996, 125(7):549-57. [PubMed 8815753]*
44. *Green DM, Cotton CA, Malogolowkin M, et al, "Treatment of Wilms Tumor Relapsing After Initial Treatment With Vincristine and Actinomycin D: A Report From the National Wilms Tumor Study Group," Pediatr Blood Cancer, 2007, 48(5):493-9. [PubMed 16547940]*
45. *Grier HE, Krailo MD, Tarbell NJ, et al, "Addition of Ifosfamide and Etoposide to Standard Chemotherapy for Ewing's Sarcoma and Primitive Neuroectodermal Tumor of Bone," N Engl J Med, 2003, 348(8):694-701. [PubMed 12594313]*
46. *Griggs JJ, Mangu PB, Anderson H, et al, "Appropriate Chemotherapy Dosing For Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline," J Clin Oncol, 2012, 30(13):1553-61. [PubMed 22473167]*
47. *Hahn BH, McMahon MA, Wilkinson A, et al, "American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis," Arthritis Care Res (Hoboken), 2012, 64(6):797-808. [PubMed 22556106]*
48. *Hahn KM, Johnson PH, Gordon N, et al, "Treatment of Pregnant Breast Cancer Patients and Outcomes of Children Exposed to Chemotherapy In utero," Cancer, 2006, 107(6):1219-26. [PubMed 16894524]*
49. *Harper L, Morgan MD, Walsh M, et al, "Pulse versus Daily Oral Cyclophosphamide for Induction of Remission in ANCA-*

Associated Vasculitis: Long-Term Follow-up," Ann Rheum Dis, 2012, 71(6):955-60. [PubMed 22128076]

50. *Hensley ML, Hagerty KL, Kewalramani T, et al, "American Society of Clinical Oncology 2008 Clinical Practice Guideline Update: Use of Chemotherapy and Radiotherapy Protectants," J Clin Oncol, 2008, 27(1):127-45. [PubMed 19018081]*
51. *Hoffman GS, Kerr GS, Leavitt RY, et al, "Wegener Granulomatosis: An Analysis of 158 Patients," Ann Intern Med, 1992, 116(6):488-98. [PubMed 1739240]*
52. *Huang H, Abraham J, Hung E, et al. Treatment of malignant pheochromocytoma/paraganglioma with cyclophosphamide, vincristine, and dacarbazine: recommendation from a 22-year follow-up of 18 patients. Cancer. 2008;113(8):2020-2028. [PubMed 18780317]*
53. *Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol. 2000;130(4):492-513. [PubMed 11024423]*
54. *Janus N, Thariat J, Boulanger H, et al, "Proposal for Dosage Adjustment and Timing of Chemotherapy in Hemodialyzed Patients," Ann Oncol, 2010, 21(7):1395-403. [PubMed 20118214]*
55. *Jayne D, Rasmussen N, Andrassy K, et al, "A randomized Trial of Maintenance Therapy for Vasculitis Associated With Antineutrophil Cytoplasmic Autoantibodies," N Engl J Med, 2003, 349(1):36-44. [PubMed 12840090]*
56. *Kantarjian HM, O'Brien S, Smith TL, et al, "Results of Treatment With Hyper-CVAD, A Dose-Intensive Regimen, in Adult Acute Lymphocytic Leukemia," J Clin Oncol, 2000, 18(3): 547-61. [PubMed 10653870]*
57. *Keating MJ, O'Brien S, Albitar M, et al, "Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab as Initial Therapy for Chronic Lymphocytic Leukemia," J Clin Oncol, 2005, 23(18):4079-88. [PubMed 15767648]*
58. *Kelly KM, Sposto R, Hutchinson R, et al, "BEACOPP Chemotherapy is a Highly Effective Regimen in Children and Adolescents With High-Risk Hodgkin lymphoma: A Report from the Children's Oncology Group," Blood, 2011, 117(9):2596-603. [PubMed 21079154]*
59. *Kennedy R, Groepper D, Tagen M, et al. Stability of Cyclophosphamide in Extemporaneous Oral Suspensions. Ann Pharmacother. 2010, 44(2):295-301. [PubMed 20103616]*
60. *Khan ML, Reeder CB, Kumar SK, et al, "A Comparison of Lenalidomide/Dexamethasone versus Cyclophosphamide/Lenalidomide/Dexamethasone versus Cyclophosphamide/Bortezomib/Dexamethasone in Newly Diagnosed Multiple Myeloma," Br J Haematol, 2012, 156(3):326-33. [PubMed 22107129]*
61. *Khouri IF, McLaughlin P, Saliba RM, et al, "Eight-Year Experience With Allogeneic Stem Cell Transplantation for Relapsed Follicular Lymphoma After Nonmyeloablative Conditioning With Fludarabine, Cyclophosphamide, and Rituximab," Blood, 2008, 111(12):5530-6. [PubMed 18411419]*
62. *Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012;119(19):4375-4382. [PubMed 22422823]10.1182/blood-2011-11-395749*
63. *Kushner BH, LaQuaglia MP, Bonilla MA, et al, "Highly Effective Induction Therapy for Stage 4 Neuroblastoma in Children Over 1 Year of Age," J Clin Oncol, 1994, 12(12):2607-13. [PubMed 7527454]*
64. *Lacasce A, Howard O, Fisher D, et al. Modified magrath regimens for adults with Burkitt and Burkitt-like lymphomas: preserved efficacy with decreased toxicity. Leuk Lymphoma. 2004;45(4):761-767. [PubMed 15160953]*
65. *Langford CA, "Complications of Cyclophosphamide Therapy,"Eur Arch Otorhinolaryngol, 1997, 254(2):65-72. [PubMed 9065658]*
66. *Larson RA, Dodge RK, Burns CP, et al, "A Five-Drug Remission Induction Regimen With Intensive Consolidation for Adults With Acute Lymphoblastic Leukemia: Cancer and Leukemia Group B Study 8811," Blood, 1995, 85(8):2025-37. [PubMed 7718875]*
67. *Lehman TJ and Onel K, "Intermittent Intravenous Cyclophosphamide Arrests Progression of the Renal Chronicity Index in Childhood Systemic Lupus Erythematosus," J Pediatr, 2000, 136(2):243-7. [PubMed 10657833]*
68. *Levine MN, Bramwell VH, Pritchard KI, et al, "Randomized Trial of Intensive Cyclophosphamide, Epirubicin, and Fluorouracil Chemotherapy Compared With Cyclophosphamide, Methotrexate, and Fluorouracil in Premenopausal Women With Node-Positive Breast Cancer. National Cancer Institute of Canada Clinical Trials Group," J Clin Oncol, 1998, 16(8):2651-8. [PubMed 9704715]*

69. *Loibl S, von Minckwitz G, Gwyn K, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. Cancer. 2006;106(2):237-246. [PubMed 16342247]*

70. *Lombel RM, Gipson DS, Hodson EM. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol. 2013;28(3):415-426. [PubMed 23052651]*

71. *Lurain JR, Singh DK, Schink JC. Primary treatment of metastatic high-risk gestational trophoblastic neoplasia with EMA-CO chemotherapy. J Reprod Med. 2006;51(10):767-772. [PubMed 17086804]*

72. *Magrath I, Adde M, Shad A, et al, "Adults and Children With Small Non-Cleaved-Cell Lymphoma Have a Similar Excellent Outcome When Treated With the Same Chemotherapy Regimen," J Clin Oncol, 1996, 14(3):925-34. [PubMed 8622041]*

73. *Malik SW, Myers JL, DeRemee RA, et al, "Lung Toxicity Associated With Cyclophosphamide Use. Two Distinct Patterns," Am J Respir Crit Care Med, 1996, 154(6 Pt 1):1851-6. [PubMed 8970380]*

74. *Marcolongo R, Russo R, Laveder F, et al. Immunosuppressive therapy prevents recurrent pericarditis. J Am Coll Cardiol. 1995;26(5):1276-1279. [PubMed 7594043]*

75. *Mok CC, Lau CS, and Wong RW, "Risk Factors for Ovarian Failure in Patients With Systemic Lupus Erythematosus Receiving Cyclophosphamide Therapy," Arthritis Rheum, 1998, 41(5):831-7. [PubMed 9588734]*

76. *Morgan C, Tillett T, Braybrooke J, et al, "Management of Uncommon Chemotherapy-Induced Emergencies," Lancet Oncol, 2011, 12(8):806-14. [PubMed 21276754]*

77. *Murdych T and Weisdorf DJ, "Serious Cardiac Complications During Bone Marrow Transplantation at the University of Minnesota, 1977-1997," Bone Marrow Transplant, 2001, 28(3):283-7. [PubMed 11535997]*

78. *Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117(16):4190-4207. [PubMed 21325604]*

79. *Page RL 2nd, O'Bryant CL, Cheng D, et al; American Heart Association Clinical Pharmacology and Heart Failure and Transplantation Committees of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Drugs That May Cause or Exacerbate Heart Failure: A Scientific Statement From the American Heart Association [published correction appears in Circulation. 2016;134(12):e261]. Circulation. 2016;134(6):e32-e69. [PubMed 27400984]*

80. *Peccatori FA, Azim HA Jr, Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-167. [PubMed 23813932]*

81. *Petri M, Brodsky RA, Jones RJ, et al, "High-Dose Cyclophosphamide versus Monthly Intravenous Cyclophosphamide for Systemic Lupus Erythematosus: A Prospective Randomized Trial," Arthritis Rheum, 2010, 62(5):1487-93. [PubMed 20131296]*

82. *Procytox (cyclophosphamide) [product monograph]. Mississauga, Ontario, Canada: Baxter; September 2012.*

83. *Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168-186. [PubMed 19846889]*

84. *Pujari SS, Kempen JH, Newcomb CW, et al. Cyclophosphamide for ocular inflammatory diseases. Ophthalmology. 2010;117(2):356-365. [PubMed 19969366]*

85. *Reece DE, Barnett MJ, Connors JM, et al, "Intensive Chemotherapy With Cyclophosphamide, Carmustine, and Etoposide Followed by Autologous Bone Marrow Transplantation for Relapsed Hodgkin's Disease," J Clin Oncol, 1991, 9(10):1871-9. [PubMed 1919637]*

86. *Robak T, Dmoszynska A, Solal-Céligny P, et al, "Rituximab Plus Fludarabine and Cyclophosphamide Prolongs Progression-Free Survival Compared With Fludarabine and Cyclophosphamide Alone in Previously Treated Chronic Lymphocytic Leukemia," J Clin Oncol, 2010, 28(10):1756-65. [PubMed 20194844]*

87. *Roila F, Molassiotis A, Herrstedt J, et al; participants of the MASCC/ESMO Consensus Conference Copenhagen 2015. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol. 2016;27(suppl 5):v119-v133. [PubMed 27664248]*

88. *Rubie H, Michon J, Plantaz D, et al, "Unresectable Localized Neuroblastoma: Improved Survival After Primary Chemotherapy Including Carboplatin-Etoposide. Neuroblastoma Study Group of the Societe Francaise d'Oncologie Pediatrique (SFOP)," Br J Cancer, 1998, 77(12):2310-7. [PubMed 9649151]*

89. *Rubie H, Plantaz D, Coze C, et al, "Localised and Unresectable Neuroblastoma in Infants: Excellent Outcome With Primary Chemotherapy. Neuroblastoma Study Group, Société Française d'Oncologie Pédiatrique," Med Pediatr Oncol, 2001, 36(1):247-50. [PubMed 11464897]*

90. *Schuchter LM, Hensley ML, Meropol NJ, et al, "2002 Update of Recommendations for the Use of Chemotherapy and Radiotherapy Protectants: Clinical Practice Guidelines of the American Society of Clinical Oncology," J Clin Oncol, 2002, 20(12):2895-903. [PubMed 12065567]*

91. *Sehn LH, Antin JH, Shulman LN, et al, "Primary Diffuse Large B-Cell Lymphoma of the Mediastinum: Outcome Following High-Dose Chemotherapy and Autologous Hematopoietic Cell Transplantation," Blood, 1998, 91(2):717-23.*

92. *Shehadeh N, Dansey R, Seen S, et al, "Cyclophosphamide-Induced Methemoglobinemia," Bone Marrow Transplant, 2003, 32(11):1109-10. [PubMed 14625586]*

93. *Slayton RE, Park RC, Silverberg SG, et al. Vincristine, Dactinomycin, and Cyclophosphamide in the Treatment of Malignant Germ Cell Tumors of the Ovary. A Gynecologic Oncology Group Study (A Final Report). Cancer. 1985;56(2):243-248. [PubMed 2988740]*

94. *Snowden JA, Pearce RM, Lee J, et al, "Haematopoietic Stem Cell Transplantation (HSCT) in Severe Autoimmune Diseases: Analysis of UK Outcomes From the British Society of Blood and Marrow Transplantation (BSBMT) Data Registry 1997-2009," Br J Haematol, 2012, 157(6):742-6. [PubMed 22533715]*

95. *Snowden JA, Saccardi R, Allez M, et al, "Haematopoietic SCT in Severe Autoimmune Diseases: Updated Guidelines of the European Group for Blood and Marrow Transplantation," Bone Marrow Transplant, 2012, 47(6):770-90. [PubMed 22002489]*

96. *Stone JH, Merkel PA, Spiera R, et al, "Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis," N Engl J Med, 2010, 363(3):221-32. [PubMed 20647199]*

97. *Thompson JA, Fisher RI, Leblanc M, et al, "Total Body Irradiation, Etoposide, Cyclophosphamide, and Autologous Peripheral Blood Stem-Cell Transplantation Followed by Randomization to Therapy With Interleukin-2 Versus Observation for Patients With Non-Hodgkin Lymphoma: Results of a Phase 3 Randomized Trial by the Southwest Oncology Group (SWOG 9438)," Blood, 2008, 111(8):4048-54. [PubMed 18256325]*

98. *US Department of Health and Human Services; Centers for Disease Control and Prevention; National Institute for Occupational Safety and Health. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2016. http://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf. Updated September 2016. Accessed October 5, 2016.*

99. *von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol. 1999;17(2):658-667. [PubMed 10080612]*

100. *Wheeler C, Antin JH, Churchill WH, et al, "Cyclophosphamide, Carmustine and Etoposide With Autologous Bone Marrow Transplantation in Refractory Hodgkin's Disease and Non-Hodgkin's Lymphoma: A Dose-Finding Study," J Clin Oncol, 1990, (4):648-56. [PubMed 2313334]*

101. *Xie H, Griskevicius L, Stahle L, et al, "Pharmacogenetics of Cyclophosphamide in Patients With Hematologic Malignancies," Eur J Pharm Sci, 2006, 27(1):54-61. [PubMed 16183265]*

Topic 9308 Version 187.0