CYCLOPHOSPHAMIDE:

Class: Antineoplastic Agent, Alkylating Agent
Indications: -Single agent for solid tumors -Acute lymphoblastic leukemia -Breast cancer -Chronic lymphocytic leukemia -Ewing's Gestational trophoblastic tumors, high-risk Granulomatosis with polyangiitis -Hodgkin lymphoma -Multiple myeloma - Non-Hodgkin lymphoma -Lupus nephritis -Transplant conditioning

Available dosage form in the hospital: 1 G VIAL || 500MG VIAL || 50MG TAB

Trade Names: Procytox , Alkyloxan (SG); Alkyroxan (KP); Ciclifen (PY); Cicloxal (ES); Cryofaxol (MX); Cycloblastin

Dosage: Details concerning dosing in combination regimens should also be consulted. Antiemetics may be recommended (emetogenic potential varies by dose and combination therapy).

-*U.S. labeling:*

-**Single agent for solid tumors:**

-I.V.: 40-50 mg/kg in divided doses over 2-5 days or 10-15 mg/kg every 7-10 days or 3-5 mg/kg twice weekly

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

-*Canadian labeling:*

-I.V.: Initial: 40-50 mg/kg (1500-1800 mg/m^2) administered as 10-20 mg/kg/day over 2-5 days; Maintenance: 10-15 mg/kg (350-550 mg/m^2) every 7-10 days or 3-5 mg/kg (110-185 mg/m^2) twice weekly

-Oral: Initial 1-5 mg/kg/day (depending on tolerance); Maintenance: 1-5 mg/kg/day

-*Indication specific and/or unlabeled uses/dosing:*

-**Acute lymphoblastic leukemia (unlabeled dosing): Multiple-agent regimens:**

-*Hyper-CVAD regimen:* I.V.: 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)

-*Larson (CALGB8811) regimen:* I.V.:

-Adults <60 years: Induction phase: 1200 mg/m^2 on day 1 of a 4-week cycle; Early intensification phase: 1000 mg/m^2 on day 1 of a 4-week cycle (repeat once); Late intensification phase: 1000 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: 1000 mg/m^2 on day 1 of a 4-week cycle (repeat once); Late intensification phase: 1000 mg/m^2 on day 29 of an 8-week cycle (Larson, 1995)

-**Breast cancer (unlabeled dosing):**

-*AC regimen:* I.V.: 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 1-14 every 28 days (in combination with epirubicin and fluorouracil) for 6 cycles (Levine, 1998)

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

-**Chronic lymphocytic leukemia (unlabeled dosing):** I.V.: 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's sarcoma (unlabeled use):** I.V.: 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)

-**Gestational trophoblastic tumors, high-risk (unlabeled use):** I.V.: 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)

-**Granulomatosis with polyangiitis (GPA; Wegener's granulomatosis) (unlabeled use; in combination with glucocorticoids):**

-*Low-dose:* Oral: 1.5-2 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:* I.V.: 15 mg/kg (maximum dose: 1200 mg) every 2 weeks for 3 doses, followed by maintenance pulses of either 15 mg/kg I.V. (maximum dose: 1200 mg) every 3 weeks or 2.5-5 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 (unlabeled dosing):** I.V.:

-*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:* 1200 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 (unlabeled 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)

-**Non-Hodgkin lymphoma (unlabeled dosing):** I.V.:

-*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 6-8 cycles (Garcia-Suarez, 2007)

-*CODOX-M/IVAC (Burkitt's lymphoma):* Cycles 1 and 3 (CODOX-M): 800 mg/m^2 on day 1, followed by 200 mg/m^2 on days 2-5 (in combination with vincristine, doxorubicin, and methotrexate); CODOX-M alternates with IVAC (etoposide, ifosfamide, and cytarabine) for a total of 4 cycles (Magrath, 1996)

-**Lupus nephritis (unlabeled use):** I.V.: 500 mg once every 2 weeks for 6 doses or 500-1000 mg/m^2 once every month for 6 doses (Hahn, 2012) or 500-1000 mg/m^2 every month every month for 6 months, then every 3 months for a total of at least 2.5 years (Austin, 1986; Gourley, 1996)

-**Transplant conditioning (unlabeled use):** I.V.:

-*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)
- 1800 mg/m^2/day for 4 days beginning 7 days prior to transplant (in combination with etoposide and carmustine.

Geriatric
Refer to adult dosing; adjust for renal clearance.

Renal Impairment:
-***U.S. labeling:*** No adjustment provided in the manufacturer's labeling (use with caution; elevated levels of metabolites may occur).
-***Canadian labeling:***
-Mild impairment: No dosage adjustment provided in manufacturer's labeling
-Moderate impairment: Dose reduction may be necessary; manufacturer's labeling does not provide specific dosing recommendations
-Severe impairment: Use is contraindicated.
-*The following adjustments have also been recommended:*
-Aronoff, 2007: Children and Adults:
- $Cl_{cr} \geq 10$ 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

Hepatic Impairment:
The pharmacokinetics of cyclophosphamide are not significantly altered in the presence of hepatic insufficiency.
-***U.S. labeling:*** No dosage adjustment provided in the manufacturer's labeling.
-***Canadian labeling:***
-Mild-to-moderate impairment: No dosage adjustment provided in the manufacturer's labeling.
-Severe impairment: Use is contraindicated.
-*The following adjustments have been recommended* (Floyd, 2006):
-Serum bilirubin 3.1-5 mg/dL or transaminases >3 times ULN: Administer 75% of dose.
-Serum bilirubin >5 mg/mL: Avoid use.

Dosing: Obesity
*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).

Dosing: Adjustment for Toxicity

-*Hematologic toxicity:* May require dose reduction or treatment interruption; Canadian labeling recommends reducing initial dose by 30% to 50% if bone marrow function compromised (due to prior radiation therapy, prior chemotherapy, or tumor infiltration)

-*Hemorrhagic cystitis, severe:* Discontinue treatment

Common side effect:

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

Endocrine & metabolic: Amenorrhea, azoospermia, gonadal suppression, oligospermia, oogenesis impaired, sterility

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

Genitourinary: Hemorrhagic cystitis

Hematologic: Anemia, leukopenia (dose-related; recovery: 7-10 days after cessation), myelosuppression, neutropenia, neutropenic fever, thrombocytopenia

Pregnancy Risk Factor: D