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/m²) administered as 10-20 mg/kg/day over 2-5 days; Maintenance: 10-15 mg/kg (350-550 mg/m²) every 7-10 days or 3-5 mg/kg (110-185 mg/m²) 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/m² 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/m² on day 1 of a 4-week cycle; Early intensification phase: 1000 mg/m² on day 1 of a 4-week cycle (repeat once); Late intensification phase: 1000 mg/m² on day 29 of an 8-week cycle (Larson, 1995)
    - Adults ≥60 years: Induction phase: 800 mg/m² on day 1 of a 4-week cycle; Early intensification phase: 1000 mg/m² on day 1 of a 4-week cycle (repeat once); Late intensification phase: 1000 mg/m² on day 29 of an 8-week cycle (Larson, 1995)

- Breast cancer (unlabeled dosing):
  - AC regimen: I.V.: 600 mg/m² on day 1 every 21 days (in combination with doxorubicin) for 4 cycles (Fisher, 1990)
  - CEF regimen: Oral: 75 mg/m²/day days 1-14 every 28 days (in combination with epirubicin and fluorouracil) for 6 cycles (Levine, 1998)
**CMF regimen:** Oral: 100 mg/m²/day days 1-14 every 28 days (in combination with methotrexate and fluorouracil) for 6 cycles (Levine, 1998) or I.V.: 600 mg/m² 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/m²/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/m² (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/m² on day 8 of a 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² on day 1, followed by 200 mg/m² 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/m² once every month for 6 doses (Hahn, 2012) or 500-1000 mg/m² 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/m²/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/m²/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} ≥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