PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Cyclophosphamide for Injection

solution, 500 mg / mL cyclophosphamide (in ethanol)
500 mg / mL, 1 g / 2 mL and 2 g / 4 mL single-use vials

For Intravenous use

Antineoplastic Agent

Dr. Reddy's Laboratories Ltd.,
Bachupally – 500 090
India

Imported and Distributed by:
Dr. Reddy's Laboratories Canada Inc.,
Mississauga, ON L4W 4Y1
Canada

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RECENT MAJOR LABEL CHANGES

Not applicable	

TABLE OF CONTENTS
Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Cyclophosphamide for Injection, used alone or as a component of combination therapy is indicated in adults for:

A: Frequently responsive myeloproliferative and lymphoproliferative disorders

1. Malignant lymphomas (See also **4 DOSAGE AND ADMINISTRATION**)

a) **Hodgkin's disease** [Cotswold stages II & III (massive mediastinal disease) and $IIIA_{1,2}$ - IV E]
Non-Hodgkin's lymphomas (Working Formulation. Low Grade A,B,C; Intermediate Grade D,E,F,G; High Grade H,I,J)

b) Follicular lymphoma (B,C,D)

c) Lymphocytic lymphoma (A,B,E; mixed histiocytic, C,F)
** **Note:** Type A, small diffuse and well differentiated malignant lymphocytic lymphoma is consistent with chronic lymphocytic leukemia, to be considered a heterogenous group of chronic B-cell disorders.

d) Diffuse histiocytic lymphoma (G,H)

e) Lymphoblastic lymphoma (I)

f) Burkitt's lymphoma (J)

2. Multiple Myelomas (Myeloma stages II, IIIA, IIIB) (See also **4 DOSAGE AND ADMINISTRATION**)

3. Leukemias (See also **4 DOSAGE AND ADMINISTRATION**)

a) **Chronic Lymphocytic Leukemia (CLL)**
(Rai Stages II, III, IV**) (**Binet Stages B, C**)**
NOTE: Chronic lymphocytic leukemias are considered to be a heterogenous group of chronic B-cell disorders.

b) **Chronic Myelogenous Leukemia (CML)**
(Ineffective in acute blastic crises)

c) **Acute Myelogenous Leukemia (AML) (M0-M7)**
(Also called acute nonlymphocytic leukemia)
Acute Myelomonocytic Leukemia (AMML) (Type M4)

4. **Mycosis Fungoides (Advanced disease)** (Stages III, IVA, IVB) (See also **4 DOSAGE AND ADMINISTRATION**)

B: Frequently responsive solid malignancies (See also **4 DOSAGE AND ADMINISTRATION**)

1. **Neuroblastoma** (in patients with disseminated disease, Stage IV)

2. **Carcinoma of the Breast** (Stages II-IV)

3. **Retinoblastoma** (St.Jude Stages II-IV)

C: Malignant neoplasms of the lung (T N M Staging**)** (See also **4 DOSAGE AND ADMINISTRATION**)

Frequently responsive

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): In elderly patients, monitoring for toxicities and the need for dose adjustment should reflect the higher frequency of decreased hepatic, renal, cardiac, or other organ function, and concomitant diseases or other drug therapy in this population.

2 CONTRAINDICATIONS

Cyclophosphamide is contraindicated in:

- Patients who are hypersensitive to this drug or its metabolites, alone or as part of combination chemotherapy or to any ingredient in the formulation, including any non-medical ingredient, or component of the container. For a complete listing, See **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.
- Patients with urinary outflow obstructions
- Patients with severe myelosuppression
- Patients with severe renal impairment
- Patients with severe hepatic impairment
- Patients with an active infection, particularly *varicella zoster* infection
- Patients with severe immunosuppression
- Pediatric population (<18 years of age)
- Pregnant women
- Breast feeding women

- Asian patients with ALDH2 mutation

In combined chemotherapy regimen, the contraindications for each individual drug must be identified.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Cyclophosphamide is a potent drug and should be used only by physicians experienced with cancer chemotherapeutic drugs.**
- **Secondary Malignancy (see 7 Warnings and Precautions).**
- **The patient's hematologic, hepatic and urinary profile must regularly be monitored.**
- **Acute cardiac toxicity after a single dose of cyclophosphamide (see 7 Warnings and Precautions).**
- **Severe QT prolongation associated with ventricular tachyarrhythmia (see 7 Warnings and Precautions).**
- **Hepatotoxicity (see 7 Warnings and Precautions).**
- **Severe myelosuppression: Cyclophosphamide should not be administered to patients with a leukocyte count below 2500 cells/microliter (cells/ mm^3) and / or a platelet count below 50,000 cells/microliter (cells/mm^3) (see 7 Warnings and Precautions).**
- **Urotoxicity (see 7 Warnings and Precautions).**
- **Patients with renal impairment (see 7 Warnings and Precautions).**
- **Acute pulmonary toxicity after a single dose of cyclophosphamide (see 7 Warnings and Precautions).**
- **Fulminating anaphylaxis (with fatal outcome) (see 7 Warnings and Precautions).**
- **Drug-drug interaction with depolarizing muscle relaxants causes inhibition of cholinesterase activity (see 9 Drug-Drug Interactions section).**
- **Live vaccines may lead to vaccine-induced infection in patients on cyclophosphamide.**
- **Alcohol content (see 7 Warnings and Precautions).**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Cyclophosphamide should be administered only by physicians experienced with this drug.

Dosage must be individualized: Doses and duration of treatment and / or treatment intervals depend on the therapeutic indication, the scheme of a combination therapy, the patient's general state of health and organ function, and the results of laboratory

monitoring (in particular, blood cell monitoring). In combination with other cytostatics of similar toxicity, a dose reduction or extension of the therapy-free intervals may be necessary. Use of hematopoiesis stimulating agents (colony-stimulating factors and erythropoiesis stimulating agents) may be considered to reduce the risk of myelosuppressive complications and / or help facilitate the delivery of the intended dosing.

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 should be administered in the morning. Prophylactic treatment with mesna is recommended for protection of the bladder.

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

Geriatrics (> 65 years of age): In elderly patients, monitoring for toxicities and the need for dose adjustment should reflect the higher frequency of decreased hepatic, renal, cardiac, or other organ function, and concomitant diseases or other drug therapy in this population.

4.2 Recommended Dose and Dosage Adjustment

INITIAL LOADING DOSE: Cyclophosphamide for Injection
Patients with normal hematologic and bone marrow function:
Adults: i.v. 40-50 mg/Kg (1.5-1.8 g/m^2) as 10 to 20 mg/Kg/day for 2-5 days
Patients with compromised bone marrow function due to prior radiation therapy, poly-chemotherapy, or tumour cell infiltration, must have their initial loading dose reduced by 30-50%. Dosage adjustment must also be considered for children and adults with concurrent disease or special conditions.

Morning administration of Cyclophosphamide for Injection is recommended.

The leukocyte count generally serves as a guide to dosage adjustments, and maintaining a range of 2500-4000 cells/mm^3 is recommended to possibly avoid infection.

The above initial loading doses may lead to transient or more persistent reduction to 200 cells/mm^3. **The patient's hematologic profile must carefully be monitored.**

MAINTENANCE DOSE: Cyclophosphamide for Injection

It is generally advisable to administer the largest maintenance dose that can reasonably be tolerated by the patient, unless the disease is unusually sensitive to cyclophosphamide.

Adults:	i.v.	10-15 mg/Kg (350-550 mg/m^2) every 7-10 days
	i.v.	3- 5 mg/Kg (110-185 mg/m^2) twice weekly

Concurrent disease, special conditions including performance index must lead to dosage adjustment.

COMBINATION CHEMOTHERAPY REGIMEN

NOTE: These recommendations are not based on Phase III registration trials. Due to constant new developments in cancer chemotherapy, the following presentation can only be viewed as an example of effective treatments. Treatment centre-specific dose and schedule variations, addition of surgery, irradiation and other treatment modalities were not included; descriptions of treatment regimens involving chemotherapy with cyclophosphamide alone or as component of combination chemotherapy is the focus of this presentation.

When deciding upon a particular treatment regimen, the literature must carefully be reviewed.

As with monotherapy, it is advisable that treatment-related emergency measures and equipment, including pathology-specific antibiotics be physically present during combination chemotherapy.

It should be noted that regular and high-dose cyclophosphamide as monotherapy or as component of polychemotherapy are being effectively used in patients resistant to first line treatment such as melphalan or busulfan. Objective responses in a variety of different forms of cancer, plus its relative platelet-sparing effect make cyclophosphamide an alternate drug of choice. Cyclophosphamide as 60 mg/Kg i.v. for 2 days may be administered for bone marrow transplant conditioning. In patients with multiple transfusions, cyclophosphamide is not adequately IMMUNOSUPPRESSIVE, requiring the addition of AT to the retransplant cytoreduction conditioning.

HODGKIN'S DISEASE:

Patients with relapsed Hodgkin's disease and presenting marrow abnormality

C	Cyclophosphamide	1.5 g/m^2 i.v. daily for 4 consecutive days
B	Carmustine (BCNU)	300 mg/m^2 i.v. for 1 day
V	Etoposide (VP-16)	100-125 mg/m^2 i.v. b.i.d. for 3 consecutive days

PSCT Autologous peripheral stem cell transplantation i.v. following **CBV** administration: All blood products were irradiated prior to use. Mesna or continuous bladder irrigation was used to prevent hemorrhagic cystitis.

Patients with relapsed Hodgkin's disease

C	Cyclophosphamide	1.5 g/m^2 i.v. daily (days -6 to -3)
B	Carmustine(BCNU)	300 mg/m^2 i.v. for 1 day (day -6)
V	Etoposide (VP-16)	125 mg/m^2 i.v. b.i.d. (days -6 to -4)

ABMT Autologous bone marrow transplantation i.v. on day 0, 3 days after end of chemotherapy
rhG-CSF 60 mcg/Kg/day (Continuous increase or decrease of AGC = Absolute granulocyte count requires dose adjustment of rhG-CSF) for a maximum of 28 days, beginning on day 1
Note: For this treatment regimen, all patients received 1 day prior to commencement of chemotherapy 1.0 g oral phenytoin sodium, followed by 300 mg daily for 4 days as prophylaxis against seizures.

Patients with resistant relapsed Hodgkin's disease
C Cyclophosphamide 1.5 g/m^2 i.v. daily (days 1-4)
B Carmustine (BCNU) 300 mg/m^2 i.v. on day 1
V Etoposide (VP-16) 150 mg/m^2 i.v. daily (days 1-3)
ABMT Autologous bone marrow transplantation on day 7

Patients with resistant relapsed Hodgkin's disease
C Cyclophosphamide 3.0 g/m^2 i.v. days 1 and 2
B Carmustine (BCNU) 200 mg/m^2 i.v. days 1-4
V Etoposide (VP-16) 250 mg/m^2 i.v. days 1-4
ABMT Autologous bone marrow transplantation on day 7

Patients with resistant relapsed Hodgkin's disease
C Cyclophosphamide 1.8 g/m^2 i.v. daily (days 1-4)
B Carmustine (BCNU) 600 mg/m^2 i.v. on day 5
V Etoposide (VP-16) 400 mg/m^2 i.v. b.i.d. (days 1-3)
ABMT Autologous bone marrow transplantation on day 7
(With / without radiation therapy)

Patients with resistant relapsed Hodgkin's disease
C Cyclophosphamide 1.8 g/m^2 i.v. daily (days -7 to -4)
B Carmustine(BCNU) 600 mg/m^2 i.v. on day -3
V Etoposide(VP-16) 400 mg/m^2 i.v. b.i.d. (days -7 to -4)
ABMT Autologous bone marrow transplant on day 0.

Patients with refractory Hodgkin's disease and non-Hodgkin's lymphoma
(Maximum-tolerated dose = **MTD**)
C Cyclophosphamide 0.9 g/m^2 i.v. b.i.d. (days -7 to -4)
B Carmustine(BCNU) 450 mg/m^2 i.v. bolus on day -7
V Etoposide(VP-16) 250 mg/m^2 i.v. b.i.d. (days -7 to -4)
ABMT Unpurged autologous bone marrow transplant

Other treatments for Hodgkin's disease containing cyclophosphamide
CVPP
C Cyclophosphamide 300 mg/m^2 i.v. on days 1 and 8
V Vinblastine 10 mg/m^2 i.v. on days 1, 8 and 15
P Procarbazine 100 mg/m^2 **p.o.** on days 1 to 15

P	Prednisone	40 mg/m^2 **p.o.** on days 1 to 15

NOTE: Repeat the cycle every 28 days. Prednisone is given in cycles 1 and 4 only

14-year follow-up results:

CVPP

C	Cyclophosphamide	300 mg/m^2 i.v. on days 1 and 8
V	Vinblastine	10 mg/m^2 i.v. on days 1, 8, and 15
P	Procarbazine	100 mg/m^2 **p.o**. on days 1 to 15
P	Prednisone	40 mg/m^2 **p.o.** on days 1 to 15 (**Cycles 1 and 4** only)

NOTE: Repeat cycles every 42 days for a minimum of six cycles. Patients in CR after 6 or more cycles of **CVPP** continue to receive **CVPP** at 2-4- month intervals as maintenance therapy for a median period of 34 months.

NON-HODGKIN'S LYMPHOMA

Since the acute risks of multi-agent systemic chemotherapy include myelosuppression, possible hemorrhage, and infection, use of transplantation of bone marrow, peripheral stem cell support, various colony-stimulating factors and pathology-specific antibiotics should be considered prior to chemotherapy, to speed up the patient's recovery.

COMP Induction

Cyclophosphamide	1.2 g/m^2 i.v. day 1
Vincristine	2.0 mg/m^2 i.v. (maximum dose, 2.0 mg) days 3, 10, 17, and 24
Methotrexate	6,25 mg/m^2 **i.th.** days 5, 31, and 34
Methotrexate	300 mg/m^2 i.v. (60% of dose as i.v. push, 40% as 4-h infusion on day 12)
Prednisone	60 mg/m^2 **p.o.** (maximum dose 60 mg) days 3-30

COMP Maintenance

Cyclophosphamide	1 g/m^2 i.v. day 1
Vincristine	1.5 g/m^2 (maximum dose 2.0 mg) i.v. days 1 and 4
Methotrexate	6.25 mg/m^2 **i.th.** day 1 (excluded from first maintenance cycle)
Methotrexate	300 mg/m^2 i.v. (60% of dose as i.v. push, 40% as 4-h infusion) on day 15
Prednisone	60 mg/m^2 **p.o.** (maximum dose 60 mg) days 1-5 (excluded from first maintenance cycle)

NOTE: Repeat maintenance cycle every 28 days

Adult advanced-stage intermediate- or high-grade Non-Hodgkin's lymphomas:

CHOP

C	Cyclophosphamide	750 mg/m^2 i.v. on day 1
H	Hydroxydaunorubicin (Doxorubicin)	50 mg/m^2 i.v. on day 1
O	Oncovin (Vincristine)	1.5 mg/m^2 i.v.(max.2 mg/m^2) on day 1
P	Prednisone	100 mg/m^2 **p.o.** on days 1 to 5

In a large phase III comparison of CHOP vs. third-generation regimens (m-BACOD, ProMACE- CytaBOM, MACOP-B), CHOP resulted in similar failure-free and overall survival rates with lower severe toxicity.

LNH-84 Induction phase

Doxorubicin	75 mg/m^2 *i.v*. on day 1
Cyclophosphamide	1.2 g/m^2 *i.v.* on day 1
Vindesine	2 mg/m^2 *i.v.* on days 1 and 5
Bleomycin	10 mg *p.o*. on days 1 and 5
Methylprednisolone	60 mg/m^2 on days 1 and 5
Methotrexate	12 mg **i.th.** once per course

NOTE: Courses are given every 15 days, or when polymorphonuclear neutrophils exceed 1500/mcL. Total therapy (induction followed by consolidation and final intensification course) requires 8 months.

F-MACHOP

Vincristine	0.5 mg/m^2 i.v. at time 0 and at 12 hours on day 1
Cyclophosphamide	800 mg/m^2 i.v. at 36 hours (i.e., middle of day 2)
5-Fluorouracil	15 mg/Kg continuous i.v. infusion starting at 36 hours for 6 hours
Cytarabine	1 g/m^2 by continuous i.v. infusion for 6 hours immediately following 5-FU infusion
Doxorubicin	60 mg/m^2 i.v. at 48 hours (end of day 2)
Methotrexate	500 mg/m^2 by continuous i.v. infusion for 6 hours beginning at hour 60 (middle of day 3)
Prednisone	60 mg/m^2 orally from day 1 to day 14
Leucovorin	20 mg/m^2 i.v. 18 hours after methotrexate infusion, and repeated every 12 hours for four doses

NOTE: Prophylactic **i.th.** methotrexate, 12 mg total dose, plus cytarabine, 30 mg/m^2 is given to patients considered at high risk of CNS infiltration (advanced stage, marrow involvement, less than 30 years of age) on day 10 of each course. A course is administered every 3 or 4 weeks for a total of 6 cycles. During the last three cycles, the dose of doxorubicin is reduced to 40 mg/m^2 and that of methotrexate to 300 mg/m^2.

PRO-MACE-CYTABOM

Cyclophosphamide	650 mg/m^2 i.v. on day 1
Doxorubicin	25 mg/m^2 i.v. on day 1
Etoposide	120 mg/m^2 i.v. over 60-minutes on day 1
Prednisone	60 mg/m^2 p.o. on days 1 to 14
Cytarabine	300 mg/m^2 i.v. on day 8
Bleomycin	5 mg/m^2 i.v. on day 8
Vincristine	1.4 mg/m^2 i.v. on day 8
Methotrexate	120 mg/m^2 i.v. on day 8
Leucovorin rescue	25 mg/m^2 orally every 6 hours for four doses beginning on day 9

NOTE: Since this regimen is associated with an increased incidence of interstitial pneumonia with four related deaths reported, all patients now receive prophylactic trimethoprim- sulfamethoxazole as 2 tablets or 1 double-strength tablet twice daily.

NOTE: The next cycle begins on day 22. At least 6 cycles, two cycles beyond a complete remission are given.

PRO-MACE-CYTABOM chemotherapy is reported to produce at least 84% complete response (CR) in adult patients with diffuse aggressive lymphoma. The corresponding relapse rate (RR) is reported in these patients as 25%. The percentage of long-term survival is given as 69% after a 4.5-month duration of treatment.

COP-BLAM

Cyclophosphamide	500 mg/m^2 continuous i.v. infusion on day 1
Doxorubicin	50 mg/m^2 continuous i.v. infusion on day 1
Vincristine	1 mg/m^2 i.v. days 1-10
Prednisolone	40 mg/m^2 p.o. days 1-10
Procarbazine	100 mg/m^2 p.o. days 1-10
Bleomycin	10 mg/person continuous i.v. infusion on day 14
Lenograstim*	2mcg/Kg/day s.c. when granulocyte count <1000 x 10^9/L

Mean duration of administration of G-CSF for this trial was 5.4 days
* Glycosylated recombinant human G-CSF
NOTE: This regimen was repeated 6 times every 21 days

NOTE: Full dose of drugs for ≤ 70 years
80% of full dose of cyclophosphamide and doxorubicin for ages 71-75
70% of full dose of cyclophosphamide and doxorubicin for ages 76-79
60% of full dose of cyclophosphamide and doxorubicin for ages 79-83

Localized low grade lymphoma (Working Formulation "B"):

Risk-adapted **COP / CHOP-Bleo** combined modality

Cyclophosphamide	1000 mg/m^2 i.v. on day 1
Vincristine	1.4 mg/m^2 i.v.(max. 2.0 mg) on day 1
Bleomycin	15 units total i.v. on day 1
Prednisone	60 mg/m^2 **p.o.** daily for 5 days

Patients with extranodal involvement, bulky disease (≥ 5cm), or LDH↑:
In addition to the above COP-Bleo

Doxorubicin	50 mg/m^2 i.v. (max.450 mg/m^2 or less if cardiac toxicity) on day 1
Cyclophosphamide↓	750 mg/m^2 i.v. on day 1

NOTE: Bleomycin was not given to patients >60 years old, or to those with existing pulmonary toxicity. Therapy-related pulmonary toxicity led to removal of bleomycin. Both cyclophosphamide and doxorubicin were reduced by 20% following abdominal radiation.

NOTE: COP / CHOP-Bleo for 3 cycles Initial chemotherapy IF(Involved field) radiotherapy to supradiaphragmatic fields at a rate of 2 Gy per fraction to a total of 40 Gy in 4 weeks.

COP / CHOP-Bleo for 7 cycles to a total of 10 cycles.

MULTIPLE MYELOMAS

CYP + PRED

Cyclophosphamide	150 to 250 mg/m^2 (500 mg maximum) i.v. **or** p.o. per week
Prednisone	100 mg **p.o.** every other day.

M-2 (VMBCP)

Vincristine	0.03 mg/Kg i.v. on day 1
Carmustine	0.5 mg/Kg i.v. on day 1
Cyclophosphamide	10 mg/Kg i.v. on day 1
Melphalan	0.25 mg/Kg **p.o.** for 4 days
Prednisone	1.0 mg/Kg/day **p.o.** for 7 days, and then 0.5 mg/Kg/day **p.o.** for 7 days

NOTE: Repeat the cycle every 35 days

VMCP alternating with VCAP

V M C P

Vincristine	1.0 mg/m^2 (maximum 1.5 mg) i.v. on day 1
Melphalan	6 mg/m^2 **p.o.** on days 1 to 4
Cyclophosphamide	125 mg/m^2 **p.o.** on days 1 to 4
Prednisone	60 mg/m^2 **p.o.** on days 1 to 4

NOTE: Alternate every 3 weeks with the V C A P regimen

V C A P

Vincristine	1.0 mg/m^2 (maximum 1.5 mg) i.v. on day 1
Cyclophosphamide	125 mg/m^2 **p.o.** on days 1 to 4
Doxorubicin	30 mg/m^2 i.v. on day 1
Prednisone	60 mg/m^2 **p.o.** on days 1 to 4

Salvage treatment for VAD-resistant multiple myeloma:

HyperCVAD

Cyclophosphamide	300 mg/m^2 (over 3 hrs) b.i.d. days 1 to 3 (total 1.8 g/m^2) with at least 2 L oral fluids. Simultaneously, continuous infusion of 600 mg/m^2/day mesna for 3 days.

12 hours after completion of cyclophosphamide:

Vincristine	2.0 mg continuous infusion over 48 hours
Doxorubicin	50 mg/m^2 continuous infusion over 48 hours

Day 11:

Vincristine	2.0 mg rapid i.v. injection
Dexamethasone	20 mg/m^2 **p.o.** as single morning dose for 5 days beginning on day 1, and for 4 days beginning on day 11
G-CSF	5 mcg/Kg/day **s.c.** starting on day 6, to be repeated daily until granulocyte level >2000/mcL

Between days 8 and 18:
Ciprofloxacin 500 mg **p.o.** b.i.d.
Fluconazole 100 mg **p.o.** daily
Acyclovir 300 mg **p.o.** t.i.d.
NOTE: Patients received a second cycle of **HyperCVAD**, provided there had been a 50% reduction in myeloma protein.

Maintenance for responding patients:
Cyclophosphamide 125 mg/m^2 **p.o.** b.i.d. for 5 days every 5 weeks
Dexamethasone 20 mg/m^2 each morning for 5 days every 5 weeks
NOTE: Myeloablative treatment with autologous blood stem cell transplantation may be needed for persistent resistant disease or remission consolidation.

High-dose cyclophosphamide + GCS-F →PBPC ↑ /Multiple myeloma

Hour	**Cyclophosphamide(CP)**	**Mesna**
-30 min		20% of total dose of CP as 30 min infusion
0 h	1 g/m^2 (1 h infusion)	Same total dose of CP, continuous infusion over 24 hrs
2 h	1 g/m^2 (1 h infusion)	
4 h	1 g/m^2 (1 h infusion)	
6 h	1 g/m^2 (1 h infusion)	
8 h	1 g/m^2 (1 h infusion)	
10 h	1 g/m^2 (1 h infusion)	
12 h	1 g/m^2 (1 h infusion)	
24 h		50% of total dose of CP continuous infusion over 24 hrs

24 h G-CSF 300 mcg/day s.c.
NOTE: Start of hyperhydration at least 12 hrs before CP. The treatment protocol for 4 g/m^2 CP consists of 4 doses of CP.

Myelomatosis
ABCM
Adriamycin 30 mg/m^2 i.v. on day 1 of each 6-week cycle
BCNU 30 mg/m^2 i.v. on day 1 of each 6-week cycle
Followed on day 22 by
Cyclophosphamide 100 mg/m^2/day **p.o.**
Melphalan 6 mg/m^2/day **p.o.**
NOTE: If a neutrophil count of 1.8 x 10^9/L and a platelet count of 80 x 10^9/L has not been reached within 5 weeks of the last block of chemotherapy, the patient is treated with the following CP-weekly regimen:
Cyclophosphamide 300 mg/m^2 i.v. weekly on alternate days with
Prednisone 40 mg/m^2 **p.o.** weekly on alternate days

LEUKEMIAS
Dosage and schedule variations within each drug regimen may be necessary, depending upon stage of disease and condition of patient.

A method used to “clean” (purge) bone marrow from contaminating tumour cells prior to autologous transplantation in patients with acute nonlymphocytic leukemia, is the incubation of marrow with 4-hydroperoxycyclophosphamide,[87] or mafosfamide L-lysine salt.

Busulphan and total body irradiation combined with cyclophosphamide are frequently used as pretransplant regimen.

CBV as a conditioning regimen for allogeneic bone marrow transplantation for patients with acute leukemia.

C	Cyclophosphamide	1.5 g/m^2/day i.v. on day 1 to day 4
B	BCNU	300 mg/m^2 i.v. on day 1
V	Etoposide	100 mg/m^2 i.v. every 12 hours for 6 doses

Allogeneic bone marrow transplant from HLA-identical sibling donors.

Chronic Lymphocytic Leukemia (CLL):
NOTE: CLL's are considered to be a heterogenous group of chronic B-cell disorders, now included in the low-grade (indolent) non-Hodgkin’s lymphomas.

CVP

Cyclophosphamide	400 mg/m^2 **p.o.** on days 1 to 5
Vincristine	1.4 mg/m^2 i.v. on day 1
Prednisone	100 mg/m^2 **p.o.** on days 1 to 5

CHOP

C	Cyclophosphamide 750 mg/m^2 i.v. on day 1
H	Doxorubicin **(H**ydroxydaunorubicin**)** 50 mg/m^2 i.v. on day 1
O	Vincristine **(O**ncovin**)** 1.4 mg/m^2 i.v. on day 1
P	Prednisone 100 mg^2 **p.o.** on days 1 to 5

COP

Cyclophosphamide	400 mg/m^2 i.v. on day 1
Vincristine	1.0 mg/m^2 i.v. on day 1
Prednisone	40 mg/m^2 **p.o.** on days 1 to 10

Chronic Myelogenous Leukemia (CML)
(Ineffective in acute blastic crises)
NOTE: For patients under 50 years of age with an HLA-identical sibling, consider an allogeneic bone marrow transplant in the chronic phase.

Acute Myelogenous Leukemia (AML) (M0-M7)
Most centers suggest marrow transplantation for patients who have an appropriately matched HLA-compatible allogeneic sibling donor. Autologous marrow transplantation provides a potential transplant option for patients who lack a histocompatible donor. Whether ABMT offers an advantage over chemotherapy alone in children with AML in

first remission is currently being assessed. DNA damage and repair in patients receiving high-dose (60 mg/Kg in the evenings of days 8 and 7 before transplant) cyclophosphamide and radiation (2 Gy TBI in the morning of days 5 to 0) must be assessed, to obtain a safe interval between cyclophosphamide and irradiation.

Adult Acute Lymphoblastic Leukemia (ALL)

Induction with additional options:

Prednisone	40-60 mg/m^2/day p.o. for 21 days
Vincristine	1.4 mg/m^2 i.v. days 1, 8, 15, and 22
Daunorubicin	45 mg/m^2/day i.v. on days 1-3 or days 16-18
Cyclophosphamide	1 g/m^2 i.v. on day 1
L-Asparaginase	5000 IU/m^2/day i.m. for 10-14 days or 10000 IU/m^2 s.c. weekly for 3 weeks
Cytarabine (ara-C)	1-3 g/m^2 i.v. over 4-6 hours and given every 12 hours for 4-8 doses

Maintenance Course C of the French Multicentre Study (PAME):

Etoposide	200 mg/m^2 i.v. on day 1
Cyclophosphamide	600 mg/m^2 i.v. on day 1
Prednisone	40 mg/m^2/day p.o. on days 15 to 21
6-Mercaptopurine	50 mg/m^2/day p.o. on days 15 to 21

Reinduction Phase II of a German Multistudy Group:

Cyclophosphamide	650 mg/m^2 (maximum 1000 mg) i.v. on day 29
Cytarabine	75 mg/m^2 i.v. on days 31 to 34 and 38 to 41
Thioguanine	60 mg/m^2 p.o. on days 29 to 34

MYCOSIS FUNGOIDES (Advanced disease, Stages III, IVA, IVB)

Combined topical and systemic therapy after initial conservative topical treatment failed:

Total electron-beam radiation therapy, using rotating dual fields of between 3000 to 3200 cGy total dose to the skin for 8 to 12 weeks (skin tolerance). During the above therapy, the following 21-day cycles of parenteral combination chemotherapy were added:

Cyclophosphamide	500 mg/m^2 i.v. on day 1
Doxorubicin	50 mg/m^2 i.v. on day 1
Etoposide	100 mg/m^2 i.v. on days 1 to 3
Vincristine	1.4 mg/m^2 (maximum 2 mg) i.v. on day 1

NOTE: A total of 8 cycles for patients with stage III and IVA. A total of 16 cycles for patients with stage IVB (visceral disease), doxorubicin was omitted from the regimen after a cumulative dose of 450 mg/m^2 was reached, and cyclophosphamide was then increased to 750 mg/m^2

Other treatment combinations in addition to topical therapy:
(In advanced disease, the polychemotherapy addition may not significantly improve the outcome)

CHOP, COP, CVP (See pp. 31 for regimen detail)

FREQUENTLY RESPONSIVE SOLID MALIGNANCIES

NEUROBLASTOMA (In patients with disseminated disease, Stages III, IV & IV.S)
Combination chemotherapy regimen (myeloablative therapy included) with or without surgery and / or radiation therapy in children with disseminated neuroblastoma, included cyclophosphamide for both BMT conditioning and as regimen component, vincristine, doxorubicin, cisplatin, melphalan, vindesine, etoposide, teniposide and rescue with either allogeneic or autologous bone marrow.

The **CVD** regimen (cyclophosphamide, vincristine, dacarbazine) has been found active in advanced neuroblastoma, producing responses in 80% of children with metastatic disease. It should be noted that, based upon the neuroblastoma results, the **CVD** regimen has successfully been used in the treatment of advanced, malignant pheochromocytoma after optimization of antihypertensive therapy. Treatment strategy comparison was made, based upon the recognition that both tumours are neuroendocrine with similar clinical and biologic characteristics.

Treatment of neuroblastoma with intraspinal extension (NBL 90/SIOP):
4 alternating courses (AB) prior to surgery (removal of dumbbell neuroblastoma tumour), and 2 alternating courses postoperatively: Each course once every 21 days

Course A:

Carboplatin	200 mg/m^2 i.v. per day x 3 days
Etoposide (VP-16)	150 mg/m^2 i.v. per day x 3 days

Course B:

Cyclophosphamide	300 mg/m^2 **p.o.** or **i.v.** per day x 5 days
Vincristine	1.5 (max 2.0 mg) mg/m^2 i.v. per day on days 1 and 5
Doxorubicin	60 mg/m^2 i.v. on day 5

Neuroblastoma **CVD** and **CVDD** regimen:

Cyclophosphamide	750 mg/m^2 i.v. on day 1
Vincristine	1.5 mg/m^2 i.v. on day 5 (maximum dose 2.0 mg)
Dacarbazine (DTIC)	250 mg/m^2/day i.v. days 1 to 5

NOTE: This regimen was repeated every 22 days whenever possible.

Cyclophosphamide	750 mg/m^2 i.v. on day 1
Vincristine	1.5 mg/m^2 i.v. on day 5 (maximum dose 2.0 mg)
Dacarbazine (DTIC)	200 mg/m^2/day i.v. days 1-5
Doxorubicin (adriamycin)	40 mg/m^2 i.v. on day 3

NOTE: This regimen was repeated every 29 days whenever possible. Dose escalations for both cyclophosphamide and dacarbazine were allowed for.

OPEC

Vincristine	1.5 mg/m^2 i.v. bolus on day 0
Cyclophosphamide	600 mg/m^2 i.v. bolus on day 0
Cisplatin (sequentially timed)	100 mg/m^2 after 24 h prehydration on day 1 as bolus and followed by 10% mannitol diuresis
Teniposide (sequentially timed)	150 mg/m^2

Pheochromocytoma **CVD** regimen:

Cyclophosphamide	750 mg/m^2 i.v. on day 1
Vincristine	I.4 mg/m^2 i.v. on day 1
Dacarbazine	I.4 mg/m^2 i.v. on days 1 and 2

NOTE: 21-day cycle with either 1-week treatment delay, or appropriate dosage modifications for hematologic or neurologic toxicities. In the absence of significant hematologic toxicity, the dosage of cyclophosphamide and dacarbazine was increased by 10% each cycle until myelo-suppression was seen. All patients received their first treatment while hospitalized.

CARCINOMA OF THE BREAST

The following are standard and effective combination chemotherapy regimen, commonly used to treat breast cancer. Over 50% response rates in previously untreated patients are reported for **CAF** and **CMF** with / without additional drug components.

NOTE: Age < 50 years or > 50 years, pre- or postmenopausal status, and negative or positive axillary nodules must be part of each chemotherapy regimen design, in addition to the condition, the hematologic-, hepatic- and renal profile of the patient.

NOTE: Limited data suggest that adjuvant therapy (**FAC, CMF**) should be considered in male patients with primary breast cancer.

Cyclophosphamide	500 mg/m^2 i.v. on day 1
Adriamycin (doxorubicin)	50 mg/m^2 i.v. on day 1
5-**F**luorouracil	500 mg/m^2 i.v. on day 1

NOTE: Regimen is given every 21 days

High-dose CAF

C	600 mg/m^2 i.v. on day 1
A	60 mg/m^2 i.v. on day 1
F	600 mg/m^2 i.v. on day 1

NOTE: Courses are repeated every 28 days for 4 courses. High-dose **CAF** produces neutropenia, one must anticipate.

Oophorectomy(O) plus CAF, metastatic breast cancer in premenopausal women

O + CAF (1st cycle of CAF within 28 days of O)

C	100 mg/m^2 **p.o.** on days 1 to 14
A	30 mg/m^2 i.v. on days 1 and 8
F	500 mg/m^2 i.v. on days 1 and 8

NOTE: Each cycle restarted 29 days after the previous cycle (28 days). Cycles continued until 500 mg/m^2 doxorubicin(A) were administered.

Maintenance therapy for patients who had reached the maximum of 500 mg/m^2:
C 100 mg/m^2 **p.o.** on days 1 to 14
Methotrexate 40 mg/m^2 i.v. on days 1 and 8
F 600 mg/m^2 i.v. on days 1 and 8
Fluoxymesterone (substituting for long-term use of prednisone, due to ADRs) 10 mg b.i.d. **p.o.** on days 1 to 28

FAC

5-**F**luorouracil	500 mg/m^2 i.v. on days 1 **and 8**
Adriamycin(doxorubicin)	50 mg/m^2 i.v. on day 1
Cyclophosphamide	500 mg/m^2 i.v. on day 1

NOTE: Repeat cycle every 21 days

CMF Adjuvant

< 60 years

Cyclophosphamide	100 mg/m^2 **p.o.** on days 1 to 14
Methotrexate	40 mg/m^2 i.v. on days 1 and 8
5-**F**luorouracil	600 mg/m^2 i.v. on days 1 and 8

> 60 years

Cyclophosphamide	100 mg/m^2 **p.o.** on days 1 to 14
Methotrexate	30 mg/m^2 i.v. on days 1 and 8
5-**F**luorouracil	400 mg/m^2 i.v. on days 1 and 8

NOTE: Repeat cycle every 28 days. This regimen can also be presented as follows:

C 100 mg/m^2 **p.o.** days 1-14
M (40-60) mg/m^2 i.v. days 1 and 8
F (400-700) mg/m^2 i.v. days 1 and 8
(P) (40 mg/m^2) (**p.o.**) (days 1 to 14)

C 100 mg/m^2 **p.o.** on days 1 to 14
M 40 mg/m^2 i.v. on days 1 and 8
F 600 mg/m^2 i.v. on days 1 and 8
NOTE: This is referred to as "standard CMF" (Milan Group)

Doxorubicin followed by CMF
(4 courses **doxorubicin** followed by 8 courses of **CMF** vs 2 courses **CMF** alternated with 1 course of doxorubicin for a total of 12 courses)
Doxorubicin 75 mg/m^2 i.v. bolus every 21 days for 4 courses

Beginning with course 5
Cyclophosphamide 600 mg/m^2 i.v. day 1 and every 21 days for 8 courses
Methotrexate 40 mg/m^2 i.v. day 1 and every 21 days for 8 courses
5-**F**luorouracil 600 mg/m^2 i.v. day 1 and every 21 days for 8 courses
NOTE: This regimen is suggested as adjuvant therapy for patients with resectable breast cancer with 4 or more positive axillary nodes. If the patient becomes too neutropenic or thrombocytopenic, a 1- or 2-week therapy postponement should be initiated.

CA or AC
Cyclophosphamide 200 mg/m^2 **p.o.** days 3-6
Doxorubicin (**A**driamycin) 40 mg/m^2 i.v. on day 1
NOTE: Recycle every 3 to 4 weeks. Total doses of **A** should not exceed 450 mg/m^2

Doxorubicin (**A**driamycin) 45 mg/m^2 i.v. on day 1
Cyclophosphamide 500 mg/m^2 i.v. on day 1
NOTE: Recycle every 3 weeks. Toxicity is reported high. Total doses of **A** should not exceed 450 mg/m^2

RETINOBLASTOMA (Stage II to IV)
Chemoreduction is often employed to reduce the tumour volume to an extent that allows for focal treatment (cryotherapy, thermotherapy, plaque radiotherapy) of tumour residues. Other clinical settings where chemotherapy is considered are a high risk for or presence of metastatic disease and extraocular extensions of the tumour. Combinations of cyclophosphamide and dactinomycin, and cyclophosphamide and doxorubicin have been associated with mixed or partial responses in patients with locally extensive, regional, or distant disease. Preirradiation chemotherapy has been used for children with extensive intraocular tumours. Primary concerns are preservation of patient's vision, inhibiting tumour progression along the optic nerve, and genetic counselling of patient and patient's family.

MALIGNANT NEOPLASMS OF THE LUNG
Frequently responsive:

Small-cell lung cancer (SCLC)
Effective commonly used polychemotherapy:

CAV
Cyclophosphamide 1 g to 1.5 g/m^2 i.v. on day 1
Adriamycin (Doxorubicin) 45 to 70 mg/m^2 i.v. on day 1 (max. total dose 450 mg)
Vincristine 1-2 mg/m^2 (max. dose 2.0 mg) i.v. on day 1
NOTE: Repeat cycle every 3 weeks for up to 6 cycles

CAV alternating with **EP**
1 cycle of **CAV** at the lower of above doses with 1 cycle of **EP** every 3 weeks
Etoposide 100 mg/m^2 i.v. days 1-3
Platinum (Cisplatin) 25 mg/m^2 i.v. days 1-3

CAVE
Cyclophosphamide 1 g/m^2 i.v. on day 1
Adriamycin (Doxorubicin) 50 mg/m^2 i.v. on day 1
Vincristine 1.5 mg/m^2 i.v. on day 1
Etoposide 60 mg/m^2 i.v. days 1-5
NOTE: Repeat cycle every 3 weeks

CAE
Cyclophosphamide 1 g/m^2 i.v. on day 1
Adriamycin (Doxorubicin) 45 mg/m^2 i.v. on day 1
Etoposide 50 mg/m^2 i.v. days 1-5
NOTE: Repeat cycle every 3 weeks

4.3 Reconstitution
There is no reconstitution for Cyclophosphamide for Injection. See **Dilution for Intravenous Infusion** below for further instructions.

After Dilution:

For Direct Intravenous Injection

Withdraw the prescribed amount of Cyclophosphamide for Injection from the vial with a syringe and add to the required amount of 0.9% sodium chloride solution to give a final concentration of 20 mg/mL of cyclophosphamide.
Table 1: Dilution for Direct Intravenous Injection

Strength	Volume of concentrated Cyclophosphamide for Injection to be withdrawn	Dilute with 0.9% Sodium Chloride to the final volume	Cyclophosphamide Concentration
500 mg/mL	1 mL	25 mL	20 mg per mL
1 g/2 mL	2 mL	50 mL	
2 g/4 mL	4 mL	100 mL	

For Intravenous Infusion

Withdraw the prescribed amount of Cyclophosphamide for Injection from the vial with a syringe and dilute Cyclophosphamide for Injection to a minimum concentration of 2 mg per mL with any of the following diluents:

- 5% Dextrose Injection, USP
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- 0.9% Sodium Chloride Injection, USP

Table 2: Dilution for Intravenous Infusion

Strength	Volume of concentrated Cyclophosphamide for Injection to be withdrawn	Dilute with diluent to the final volume	Cyclophosphamide Concentration
500 mg/mL	1 mL	250 mL	2 mg per mL
1 g/2 mL	2 mL	500 mL	
2 g/4 mL	4 mL	1000 mL	

Cyclophosphamide for Injection should not be diluted with benzyl alcohol-preserved diluent solution such as bacteriostatic sodium chloride when used in children or infants, due to toxicity concerns in this age group (i.e., gasping syndrome in infants). Further, Cyclophosphamide for Injection should not be diluted with benzyl alcohol-containing diluents, as benzyl alcohol may catalyse the decomposition of cyclophosphamide. Therefore, it is recommended to dilute Cyclophosphamide for Injection with isotonic, sterile, Sodium Chloride Injection USP.

See **11 *STORAGE AND STABILITY, Stability of Solutions***
See **12 SPECIAL HANDLING INSTRUCTIONS**

4.4 Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. After dilution, this parenteral dosage form represents a colourless and clear solution. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

Intravenous administration preferably should be conducted as an infusion. To reduce the likelihood of adverse reactions that appear to be administration rate-dependent (e.g., facial swelling, headache, nasal congestion, scalp burning), cyclophosphamide should be injected or infused very slowly. Duration of the infusion also should be appropriate for the volume and type of carrier fluid to be infused.

Since it has been reported that immersion of a needle with an aluminum component into cyclophosphamide resulted in a slight darkening of the aluminum and gas production after a few days at 24°C with protection from light, it is recommended to avoid the use of utensils, needles or parts of infusion pumps made of aluminum in the presence of cyclophosphamide.

4.5 Missed Dose

If the patient misses the scheduled treatment, the next treatment should be scheduled as soon as possible

5 OVERDOSAGE

Limited information on acute overdosage of cyclophosphamide is available.

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 hematotoxicity in particular.

No specific antidote for cyclophosphamide is known.

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

Overdosage should be managed with supportive measures, including appropriate, state-of-the-art treatment for any concurrent infection, myelosuppression, or other toxicity, should it occur. Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects with cyclophosphamide overdose.

Cardiotoxicity may also occur with overdosage. In patients who received 4 to 10-day courses of cyclophosphamide with total dosage per course exceeding 140 mg/Kg or 5.2 g/m^2, cardiac damage manifested by heart failure occurred within 15 days of the initial dose. Impairment of water excretion with hyponatremia, weight gain, and inappropriately concentrated urine has been reported after cyclophosphamide doses exceeding 50 mg/Kg (2 g/m^2).

At least one fatal case of cyclophosphamide overdosage had been reported; potentially fatal cardiotoxicity was the most serious consequence of overdosage. The risk of overdose with high- dose cyclophosphamide concomitantly with radiation therapy or other potentially cardiotoxic drugs (e.g: anthracyclines) must carefully be taken into consideration.

If a cyclophosphamide solution is inadvertently administered by paravenous injection, there is usually no danger of cytostatic tissue damage since such damage is not expected before cyclophosphamide has been bioactivated in the liver. Nevertheless, if paravasation should occur, stop the infusion immediately and aspirate the paravasate with the cannula in place, irrigate the area with saline solution and immobilize the extremity.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Nonmedicinal Ingredients
Intravenous	Solution: 500 mg/mL, 1 g/2 mL and 2 g/4 mL	ethanol anhydrous

Cyclophosphamide for Injection is a clear, colorless to slight yellow sterile solution available as 500 mg/mL, 1 g/2 mL, and 2 g/4 mL in single-use vials for dilution prior to intravenous administration. Preservative free.

COMPOSITION

- Each 500 mg/mL vial contains 500 mg cyclophosphamide, and 513.5 mg ethanol anhydrous.
- Each 1 g/2 mL vial contains 1 g cyclophosphamide, and 1027 mg ethanol anhydrous.
- Each 2 g/4 mL vial contains 2 g cyclophosphamide, and 2054 mg ethanol anhydrous.

Cyclophosphamide for Injection 500 mg/mL and 1g/2 mL are packed in 2 mL clear USP Type – I tubular glass vials with a grey chloro butyl 13 mm teflon coated rubber stoppers and sealed with 13 mm red and mist grey color flip off seal respectively. It is available as one vial per carton.

Cyclophosphamide for Injection 2 g/4 mL is packed in 5 mL clear USP Type – I tubular glass vials with a grey chloro butyl 13 mm teflon coated rubber stoppers and sealed with 13 mm violet color flip off seal. It is available as one vial per carton.
Discard unused portion. The vial stopper is not made with natural-rubber latex.

See **11 STORAGE AND STABILITY**

7 WARNINGS AND PRECAUTIONS

General

Risk factors for cyclophosphamide toxicities and their sequelae described here and in other sections may constitute contraindications if cyclophosphamide is not used for the treatment of a life-threatening condition. In such situations, individual assessment of risk and expected benefits is necessary.

Prior to initiating treatment with Cyclophosphamide for Injection, it is necessary to exclude or correct any electrolyte imbalances.

Each individual component of a cyclophosphamide-containing poly-chemotherapy regimen must have its precaution profile reviewed.

Since cyclophosphamide is highly toxic with a relatively low therapeutic index, and a therapeutic response is not likely to occur without some evidence of toxicity, the drug must only be used under constant supervision of the attending physician.

Alopecia occurs commonly in patients treated with even low doses of cyclophosphamide. With large parenteral doses, considerable hair loss (5-30%, with possible total alopecia) is to be expected. The hair can be expected to grow back after or even during continued treatment; it may, however be different in texture and / or colour.

If a patient who is to undergo surgery is receiving cyclophosphamide or has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthetist should be so advised prior to surgery (See also **9 Drug-Drug Interactions section**).

In case of accidental paravenous administration of cyclophosphamide, the infusion should be stopped immediately, the extravascular cyclophosphamide solution should be aspirated with the cannula in place, and other measures should be instituted as appropriate.

Carcinogenesis and Mutagenesis
As with cytotoxic therapy in general, treatment with cyclophosphamide involves the risk of secondary tumours and their precursors as late sequelae.

The risk of developing urinary tract cancer as well as myelodysplastic alterations partly progressing to acute leukemias, or non-malignant disease in which immune processes are believed to be involved pathologically is increased. Other malignancies reported after use of cyclophosphamide or regimens with cyclophosphamide include lymphoma, thyroid cancer, and sarcomas.

In some cases, the second malignancy developed several years after cyclophosphamide treatment had been discontinued. Malignancy has also been reported after *in utero* exposure.

Urinary bladder malignancies have usually occurred in patients who previously had hemorrhagic cystitis. Animal studies demonstrate that the risk of bladder cancer can be markedly reduced by an adequate administration of mesna.

Cardiovascular
Myocarditis and myopericarditis, which may be accompanied by significant pericardial effusion and cardiac tamponade, have been reported with cyclophosphamide therapy and have led to severe, sometimes fatal congestive heart failure.

Histopathologic examination has primarily shown hemorrhagic myocarditis. Hemopericardium has occurred secondary to hemorrhagic myocarditis and myocardial necrosis.

Acute cardiac toxicity has been reported with a single dose of less than 20 mg/kg cyclophosphamide.

Following exposure to treatment regimens that included cyclophosphamide, supraventricular arrhythmias (including atrial fibrillation and flutter) as well as ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported in patients with and without other signs of cardiotoxicity.

The risk of cyclophosphamide cardiotoxicity may be increased following high doses of cyclophosphamide, in patients with advanced age, and in patients with previous radiation treatment of 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 pre-existing cardiac disease.

Driving and Operating Machinery
Due to potential adverse effects of cyclophosphamide such as dizziness, blurred vision, visual impairment, nausea and vomiting which could be symptoms of vasomotor ataxia, caution should be advised when driving or operating machinery.

Alcohol Content
Each mL of Cyclophosphamide for Injection contains 513.5 mg of ethanol anhydrous. The alcohol content in a dose of cyclophosphamide regimen may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized, including high-risk groups such as patients with hepatic impairment or epilepsy. Some medications, such as CNS depressants, pain relievers and sleep aids may interact with the alcohol in the cyclophosphamide infusion and exacerbate depression or worsen the intoxicating effects. Product may also interact with the other alcohol containing chemotherapy drugs which could be administered concomitantly with cyclophosphamide.

Patients are advised to avoid driving, operating machinery, or performing other activities that are dangerous for one to two hours after the infusion of Cyclophosphamide for Injection.

Health care professionals should consider the alcohol content of Cyclophosphamide for Injection when prescribing or administering the drug to patients when using it in conjunction with other medications.

Endocrine and Metabolism
Cyclophosphamide has been shown to be more toxic in adrenalectomized dogs. Dose adjustments of Cyclophosphamide for Injection may be necessary for adrenalectomized patients.

Gastrointestinal
Administration of cyclophosphamide may cause nausea and vomiting.

Current guidelines on the use of antiemetics for prevention and amelioration of nausea and vomiting should be considered.

Alcohol consumption may increase cyclophosphamide-induced vomiting and nausea.
Administration of cyclophosphamide may cause stomatitis (oral mucositis).

Current guidelines on measures for prevention and amelioration of stomatitis should be considered.

Genitourinary
Prior to initiating treatment with Cyclophosphamide for Injection, it is necessary to exclude or correct any obstructions of the efferent urinary tract, cystitis, and infections.

Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported with cyclophosphamide therapy. Bladder injury such as hemorrhagic cystitis / necrosis, fibrosis of the bladder and secondary cancer may develop in patients on long-term cyclophosphamide therapy. Should a cystitis in connection with micro-or macrohematuria appear during treatment with Cyclophosphamide for Injection, therapy must be interrupted until normalization.

Urotoxicity may mandate interruption or discontinuation of treatment.

Cystectomy may become necessary due to fibrosis, bleeding, or secondary malignancy.

Cases of urotoxicity with fatal outcomes have been reported.

Urotoxicity can occur with short-term and long-term use of cyclophosphamide. Hemorrhagic cystitis after single doses of cyclophosphamide has been reported.

Past or concomitant radiation or busulfan treatment may increase the risk for cyclophosphamide- induced hemorrhagic cystitis.

Secondary bacterial colonization of the initially abacterial cystitis may follow.

Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro / nephrotoxicity. (See also **7 Monitoring and Laboratory Tests section**)

Cyclophosphamide should not be used in patients with active urinary tract infections.

Adequate treatment with mesna and / or strong hydration to force diuresis can markedly reduce the frequency and severity of bladder toxicity. It is important to ensure that patients empty the bladder at regular intervals.

Cyclophosphamide therapy should be discontinued in instances of severe hemorrhagic cystitis.

Cyclophosphamide has also been associated with nephrotoxicity, including renal tubular necrosis.

Hyponatremia associated with increased total body water, acute water intoxication, and cases of a syndrome resembling SIADH (syndrome of inappropriate secretion of antidiuretic hormone), including those with fatal outcome, have been reported in association with cyclophosphamide administration.

Hepatic / Biliary / Pancreatic
Veno-occlusive liver disease (VOLD) has been reported in patients receiving cyclophosphamide.

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 for the development of VOLD. After cytoreductive therapy, the clinical syndrome typically develops 1 to 2 weeks after transplantation and is characterized by sudden weight gain, painful hepatomegaly, ascites, and hyperbilirubinemia / jaundice.

VOLD has also been reported to develop gradually in patients receiving long-term low-dose immunosuppressive doses of cyclophosphamide.

As a complication of VOLD, hepatorenal syndrome and multiorgan failure may develop. Fatal outcome of cyclophosphamide-associated VOLD has been reported.
Risk factors predisposing a patient to the development of VOLD with high-dose cytoreductive therapy include

- preexisting disturbances of hepatic function,
- previous radiation therapy of the abdomen,
- low performance score.

The cytostatic effect of cyclophosphamide occurs after its activation, which takes place mainly in the liver.

Severe hepatic impairment may be associated with decreased activation of cyclophosphamide. This may alter the effectiveness of cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected.

The alcohol content of Cyclophosphamide Injection should be taken into account when given to patients with hepatic impairment as alternative alcohol-free cyclophosphamide medicinal products are available.

Immune

Treatment with Cyclophosphamide for Injection may cause myelosuppression and significant suppression of immune responses. Dose modification should be considered for patients who develop bacterial, fungal or viral infections in prior cycles. Patients with active infection should not be treated with Cyclophosphamide for Injection.

Cyclophosphamide-induced myelosuppression can cause leukopenia, neutropenia, thrombocytopenia (associated with a higher risk of bleeding events), and anemia.

Severe immunosuppression has lead to serious, sometimes fatal, infections. Sepsis and septic shock have also been reported. Infections reported with cyclophosphamide include pneumonias, as well as other bacterial, fungal, viral, protozoal, and parasitic infections.

Latent infections can be reactivated. Reactivation has been reported for various bacterial, fungal, viral, protozoal, and parasitic infections.

Live vaccines should not be administered to immunocompromised patients.

Antimicrobial prophylaxis may be indicated in certain cases of neutropenia at the discretion of the managing physician.

In case of neutropenic fever, antibiotics and / or antimycotics must be given.

Caution is indicated, when administering cyclophosphamide to patients with tumor cell infiltration of bone marrow (See **4 DOSAGE and ADMINISTRATION)**.

Cyclophosphamide should not be administered to patients with a leukocyte count below 2500 cells/microliter (cells/ mm^3) and / or a platelet count below 50,000 cells/microliter (cells/mm^3).

The fall in the peripheral blood cell and thrombocyte count and the time taken to recover may increase with increasing doses of cyclophosphamide.

The nadirs of the reduction in leukocyte count and thrombocyte count are usually reached in weeks 1 and 2 of treatment. The levels of peripheral blood cell counts normalize after approximately 20 days.

Severe myelosuppression must be expected particularly in patients pretreated with and / or receiving concomitant chemotherapy and / or radiation therapy.

Monitoring and Laboratory Tests

During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly, to determine the degree of hematopoietic suppression.

Leukocyte counts must be conducted regularly during treatment: at intervals of 5-7 days when starting treatment and every 2 days if the counts drop below 3000/mm³. Daily counts may be necessary under certain circumstances. In patients receiving long-term treatment, counts every two weeks are usually sufficient. If signs of myelosuppression become evident, it is recommended to check the red blood count and the platelet count. Platelet count and hemoglobin value should be obtained prior to each administration and at appropriate intervals after administration. Urinary sediment should also be checked regularly for the presence of erythrocytes and other signs of uro / nephrotoxicity.

Urine should be examined regularly for red cells, a possible indicator for hemorrhagic cystitis.

Frequent liver function tests (LFT's) and periodic monitoring of electrolytes are advised.

Because cyclophosphamide is associated with pneumonitis and pulmonary fibrosis, monitoring of PFT's should be considered.

Due to potential QT-interval prolongation, periodic EKG's are recommended.

Peri-Operative Considerations
Cyclophosphamide may interfere with normal wound healing.

Renal
In patients with renal impairment, particularly 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 and should be considered when determining the dosage in such patients.

Reproduction Health: Female and Male Potentials
(See **7.1.1 Pregnant Women**)

- **Fertility**

  Animal data indicate that exposure of oocytes during follicular development may result in a decreased rate of implantations and viable pregnancies, and in an increased risk of malformations. This effect should be considered in case of intended fertilization or pregnancy after discontinuation of cyclophosphamide therapy. The exact duration of follicular development in humans is not known, but may be longer than 12 months.

  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

Female patients
Amenorrhea, transient or permanent, associated with decreased estrogen and increased gonadotropin secretion develops in a significant proportion of women treated with cyclophosphamide.

For older women, in particular, amenorrhea may be permanent.

Oligomenorrhea has also been reported in association with cyclophosphamide treatment.

Girls treated with cyclophosphamide who have retained ovarian function after completing treatment are at increased risk of developing premature menopause (cessation of menses before age of 40 years).

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

Boys treated with cyclophosphamide during prepubescence may develop secondary sexual characteristics normally, but may have oligospermia or azoospermia.

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.

- **Teratogenic Risk**

  Cyclophosphamide is genotoxic and mutagenic, both in somatic and in male and female germ cells.

  Women of childbearing potential should not become pregnant and should use effective contraception during the treatment with Cyclophosphamide for Injection and for at least 1 years after the end of therapy

  Men should not father a child and should use effective contraception during treatment with cyclophosphamide and for at least 6 months after the end of therapy.

Respiratory
Pneumonitis and pulmonary fibrosis have been reported during and following treatment with cyclophosphamide. Pulmonary veno-occlusive disease and other forms of pulmonary toxicity have also been reported. Pulmonary toxicity leading to respiratory failure has been reported. Prognosis for affected patients is poor.

Late onset of pneumonitis (greater than 6 months after start of cyclophosphamide) appears to be associated with a particularly high mortality. Pneumonitis may develop even years after treatment with cyclophosphamide.

Acute pulmonary toxicity has been reported after a single cyclophosphamide dose.

Sensitivity / Resistance
Anaphylactic reactions including those with fatal outcomes have been reported in association with cyclophosphamide.

Possible cross-sensitivity with other alkylating agents has been reported.

7.1 Special Populations

7.1.1 Pregnant Women*:*

Cyclophosphamide for Injection is contraindicated in pregnant women.
Cyclophosphamide crosses the placental barrier. Treatment with cyclophosphamide has a genotoxic effect and may cause fetal damage when administered to pregnant women.

Malformations have been reported in children born to mothers treated with cyclophosphamide during the first trimester of pregnancy.

Exposure to cyclophosphamide *in utero* may cause miscarriage, fetal growth retardation, and fetotoxic effects manifesting in the newborn, including leukopenia, anemia, pancytopenia, severe bone marrow hypoplasia, and gastroenteritis.

Animal data suggest that an increased risk of failed pregnancy and malformations may persist after discontinuation of cyclophosphamide.
If the patient becomes pregnant while taking this drug or after treatment, the patient should be apprised of the potential hazard to a fetus.

7.1.2 Breast-feeding
Cyclophosphamide for Injection is contraindicated in breast-feeding women.
Cyclophosphamide is passed into the breast milk. Neutropenia, thrombocytopenia, low hemoglobin, and diarrhea have been reported in children breast fed by women treated with cyclophosphamide.

7.1.3 Pediatrics
Pediatrics (<18 years of age): Cyclophosphamide for Injection is contraindicated in pediatric population.

7.1.4 Geriatrics
Geriatrics (> 65 years of age): While age-related renal and / or hepatic impairment may require cautious dose adjustment, no geriatrics-specific problems are expected to limit the usefulness of Cyclophosphamide for Injection in the elderly.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Increased risk for and severity of pneumonias (including fatal outcomes), reactivation of latent infections, malignant and benign neoplasms, progression of underlying malignancies (including fatal outcomes), different degrees of myelosuppression (sometimes with life threatening infections), leucopenia, anemia, thrombocytopenia, fulminating anaphylaxis (with fatal outcome), hypersensitivity reactions, syndrome of inappropriate antidiuretic hormone secretion, tumor lysis syndrome, hematuria, confusion, neurotoxicity (both the central and peripheral nervous system), cardiotoxicity (with fatal outcomes), hearing disorders, arterial and venous occlusive disorders with and without embolization, gastrointestinal hemorrhages, acute pancreatitis, hepatotoxicity, hepatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, skin eruption, hemorrhagic cystitis, rhabdomyolysis, sterility in both sexes, fetal malformation and toxicity (including intra-uterine death), multiorgan failure, general physical deterioration, increased lactate dehydrogenase and C-reactive protein.

NOTE*:* Many side effects of cancer chemotherapy are unavoidable, since they represent the drug's pharmacologic action. Leukopenia and thrombocytopenia are used as guidelines, among others, to aid in individual dosage titration.

8.2 Clinical Trial Adverse Reactions

The list of adverse reactions to cyclophosphamide in this document is based on postmarketing data.

8.5 Post-Market Adverse Reactions

The following is a summary of adverse reactions reported with cyclophosphamide either alone or in combination with other chemotherapeutic agents in the post marketing experience, listed by MedDRA system Organ Class (SOC), then by Preferred Term in order of severity, where feasible. In the case of a polychemotherapy regimen, the adverse reaction profile of each drug component should be reviewed.

INFECTIONS AND INFESTATIONS:

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, parasitic infections; reactivation of latent infections, including viral hepatitis, tuberculosis, JC virus with progressive multifocal leukoencephalopathy (including fatal outcomes), *Pneumocystis jiroveci*, herpes zoster, *Strongyloides*, Sepsis and Septic shock (including fatal outcomes)

NEOPLASMS, BENIGN AND MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS):

Acute leukemia (Acute myeloid leukemia, Acute promyelocytic leukemia), Myelodysplastic syndrome, Lymphoma (Non-Hodgkin’s lymphoma), Sarcomas, Renal cell carcinoma, Renal pelvis cancer, Bladder cancer, Ureteric cancer, Thyroid cancer, Treatment related

secondary malignancy, Carcinogenic effect in offspring, Tumor lysis syndrome. Additionally, progression of underlying malignancies, including fatal outcomes, have been reported.

BLOOD AND LYMPHATIC SYSTEM DISORDERS:
Myelosuppression manifested as Bone marrow failure, Pancytopenia, Neutropenia, Agranulocytosis, Granulocytopenia, Thrombocytopenia (complicated by bleeding), Leukopenia, Anemia; Febrile neutropenia, Lymphopenia, Disseminated intravascular coagulation, Hemolytic uremic syndrome (with thrombotic microangiopathy), Hemoglobin decreased

IMMUNE SYSTEM DISORDERS:
Immunosuppression, Anaphylactic shock, Anaphylactic / Anaphylactoid reaction (including fatal outcomes), Hypersensitivity reaction

ENDOCRINE DISORDERS:
Water intoxication, Syndrome of inappropriate antidiuretic hormone secretion (SIADH) with fatal outcomes.

METABOLISM AND NUTRITION DISORDERS:
Hyponatremia with fatal outcomes, Fluid retention, Anorexia, Blood glucose increased, Blood glucose decreased, tumor lysis manifested by hyperkalemia, hyperuricemia

PSYCHIATRIC DISORDERS:
Confusional state

NERVOUS SYSTEM DISORDERS:
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

EYE DISORDERS:
Blurring of Vision, Myopia**,** Visual impairment, Conjunctivitis, Lacrimation increased

EAR AND LABYRINTH DISORDERS:
Deafness, Hearing impaired, Tinnitus

CARDIAC DISORDERS:
Cardiac arrest, Ventricular fibrillation, Ventricular tachycardia, Cardiogenic shock, Pericardial effusion (progressing to cardiac tamponade), Myocardial hemorrhage, Myocardial infarction, Cardiac failure congestive (including fatal outcomes), Cardiac failure (including fatal outcomes),

Left ventricular failure, Left ventricular dysfunction, Cardiomyopathy, Myocarditis, Pericarditis, Carditis, Atrial fibrillation, Supraventricular arrhythmia, Ventricular arrhythmia, Bradycardia, Tachycardia, Palpitations, Electrocardiogram QT prolonged, Ejection fraction decreased

VASCULAR DISORDERS:
Pulmonary embolism, Venous thrombosis, Vasculitis, Peripheral ischemia, Hypertension, Hypotension, Flushing, Hot flush, Blood pressure decreased.

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS:
Pulmonary veno-occlusive disease, Acute respiratory distress syndrome, Interstitial lung disease as manifested by Pulmonary fibrosis, Respiratory failure (including fatal outcomes), Obliterative bronchiolitis, Organizing pneumonia, Alveolitis allergic, Pneumonitis;
Respiratory distress, Pulmonary hypertension, Pulmonary edema, Pleural effusion, Bronchospasm, Dyspnea, Hypoxia, Cough, Nasal congestion, Nasal discomfort, Oropharyngeal pain, Rhinorrhea, Sneezing

GASTROINTESTINAL DISORDERS:
Enterocolitis hemorrhagic, Gastrointestinal hemorrhage, Acute pancreatitis, Colitis, Enteritis, Cecitis, Mucosal ulceration, Stomatitis, Diarrhea, Vomiting, Constipation (sometimes severe), Nausea, Abdominal pain, Abdominal discomfort, Parotid gland inflammation.

HEPATOBILIARY DISORDERS:
Veno-occlusive liver disease with fatal outcomes, Cholestatic hepatitis, Cytolytic hepatitis, Hepatitis, Cholestasis; Hepatotoxicity with Hepatic failure, Hepatic encephalopathy, Ascites, Hepatomegaly, Jaundice, Blood bilirubin increased, Hepatic function abnormal, Hepatic enzymes increased (Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS:
Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Palmar-plantar erythrodysesthesia syndrome, Radiation recall dermatitis, Toxic skin eruption, Urticaria, Dermatitis, Rash, Blister, Pruritus, Erythema, Skin discoloration, Nail discoloration, Nail disorder, Alopecia (See **7 WARNINGS AND PRECAUTIONS**), Facial Swelling, Hyperhidrosis

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS:
Rhabdomyolysis, Scleroderma, Muscle spasms, Myalgia, Arthralgia

RENAL AND URINARY DISORDERS:
Renal failure, Renal tubular necrosis, Renal tubular disorder, Renal impairment, Nephropathy toxic, Hemorrhagic cystitis resulting in death, Hemorrhagic ureteritis, Bladder necrosis, Cystitis ulcerative, Bladder fibrosis, Bladder contracture, Hematuria, Nephrogenic diabetes insipidus, Cystitis, Atypical urinary bladder epithelial cells, Blood creatinine increased, Blood urea nitrogen increased

PREGNANCY, PUERPERIUM, AND PERINATAL CONDITIONS:
Premature labor

REPRODUCTIVE SYSTEM AND BREAST DISORDERS:
Infertility, Ovarian failure (atrophy, fibrosis and complete absence of follicular structure), Ovarian disorder, Ovulation disorder, Amenorrhea, Oligomenorrhea, Testicular atrophy, Azoospermia, Oligospermia, Blood estrogen decreased, Blood gonadotrophin increased

CONGENITAL, FAMILIAL AND GENETIC DISORDERS:
Intra-uterine death, Fetal malformation, Fetal growth retardation, Fetal toxicity (including myelosuppression, gastroenteritis)

GENERAL DISORDERS AND ADMINISTRATIVE SITE:
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

INVESTIGATIONS:
Blood lactate dehydrogenase increased, C-reactive protein increased

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview
Cyclophosphamide is a pro-drug that is metabolized in the liver by cytochrome P450 (CYP) enzymes (See **10.3 Pharmacokinetics**). Concomitant therapy with inducers of cyclophosphamide metabolizing enzymes (e.g. CYP 2B6, 2C9, 3A4) enhances the enzyme expression and may potentially increase the formation of metabolites responsible for cytotoxicity. In contrast, the inhibitors could interfere with cyclophosphamide activation and may alter the effectiveness of cyclophosphamide treatment.

Genetic polymorphism in the drug metabolizing enzymes CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, GSTA1, GSTP1, ALDH1A1, ALDH3A1 do not explain the inter individual variability in cyclophosphamide and 4 hydroxy cyclophosphamide pharmacokinetics. Renal impairment might increase the risk of toxicity due to increase in plasma level of cyclophosphamide and its metabolites. Severe hepatic impairment would decrease activation of cyclophosphamide.

Some medications, such as CNS depressants, pain relievers and sleep aids may interact with the alcohol in the cyclophosphamide infusion and exacerbate depression or worsen the intoxicating effects. Product may also interact with the other alcohol containing chemotherapy drugs which could be administered concomitantly with cyclophosphamide.

In some patients, alcohol may increase cyclophosphamide-induced vomiting and nausea.

Planned coadministration or sequential administration of other substances or treatments that could increase the likelihood or severity of toxic effects (by means of pharmacodynamic or pharmacokinetic interactions) requires careful individual assessment of the expected benefit and the risks. Patients being treated with cyclophosphamide and agents that reduce its activation should be monitored for a potential reduction of therapeutic effectiveness and the need for dose adjustment.

9.4 Drug-Drug Interactions

It is prudent to monitor, among others, the following drugs if administered concurrent with cyclophosphamide: Colchicine, Probenecid, Sulfinpyrazone, Chlorambucil, Mercaptopurine,

Combined or sequential use of cyclophosphamide and other agents with similar toxicities can cause combined (increased) toxic effects.

Table 4: Potential Drug-Drug Interactions

Name / Class / Category	Ref	Effect	Clinical Comment
Inducers of human hepatic and extrahepatic microsomal enzymes* (e.g., cytochrome P450 enzymes) Benzodiazepines, Carbamazepine, Chloral hydrate, Corticosteroids, Phenobarbital, Phenytoin, Rifampin	L	An increase of the concentration of cytotoxic metabolites may occur with inducers of CYP enzymes.	The potential for hepatic and extrahepatic microsomal enzyme induction must be considered in case of prior or concomitant treatment with substances known to induce an increased activity of such enzymes. Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Inhibitors of CYP isoforms* Aprepitant, Bupropion, Busulfan, Ciprofloxacin, Chloramphenicol, Fluconazole, Itraconazole, Prasugrel, Sulfonamides, Thiotepa	L	These substances may delay / reduce activation of cyclophosphamide. Reduced activation of cyclophosphamide may alter the effectiveness of cyclophosphamide treatment.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
ACE inhibitors	L	Increased hematotoxicity and / or immunosuppression may result from a combined effect of cyclophosphamide and	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.

Name / Class / Category	Ref	Effect	Clinical Comment
		ACE inhibitors. ACE inhibitors can cause leukopenia. Pancytopenia is a known ADR of the combination of cyclophosphamide and ACE-inhibitors.	
Allopurinol	L	Concurrent cyclophosphamide with allopurinol may enhance the bone marrow toxicity of cyclophosphamide.	If concurrent use is unavoidable, frequent monitoring for toxic effects is strongly recommended.
Amiodarone	L	Increased pulmonary toxicity may result from a combined effect of cyclophosphamide and amiodarone	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Amphotericin B	L	Increased nephrotoxicity may result from a combined effect of cyclophosphamide and amphotericin B	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Anthracyclines	L	Increased cardiotoxicity may result from a combined effect of cyclophosphamide and anthracyclines.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Azathioprine	L	Increased risk of hepatotoxicity (liver necrosis)	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Buproprion	L	Cyclophosphamide metabolism by CYP2B6 may inhibit buproprion metabolism.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Busulfan	L	Increased incidence of hepatic veno-occlusive disease and mucositis. Cyclophosphamide clearance has been reported to be reduced and half-life prolonged in patients who receive high-dose cyclophosphamide less than 24 hours after high-dose busulfan.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Cimetidine	L	An increase of the concentration of cytotoxic metabolites may occur.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Ciprofloxacin	L	When given prior to the	Patients receiving such combinations must

Name / Class / Category	Ref	Effect	Clinical Comment
		treatment with cyclophosphamide (used for conditioning prior to bone marrow transplantation), ciprofloxacin has been reported to result in a relapse of the underlying disease and reduced cyclophosphamide effectiveness.	be monitored closely for signs of toxicity to permit timely intervention.
Coumarins	L	Both increased and decreased warfarin effect have been reported in patients receiving warfarin and cyclophosphamide.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Cyclosporine	L	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. Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Cytarabine	L	Increased cardiotoxicity may result from a combined effect of cyclophosphamide and cytarabine.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Depolarizing muscle relaxants (e.g., succinylcholine)	L	Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity. Prolonged apnea may occur with concurrent depolarizing muscle relaxants	If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted. Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Digoxin (e.g., β-acetyldigoxin)	L	Cytotoxic treatment has been reported to impair intestinal absorption of digoxin.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Disulfiram	L	An increase of the concentration of cytotoxic metabolites may occur.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Etanercept	L	Cyclophosphamide used concomitantly with Etanercept was associated with a higher	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.

Name / Class / Category	Ref	Effect	Clinical Comment
		incidence of non-cutaneous solid malignancies.	
G-CSF, GM-CSF (granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor)	L	Reports suggest an increased risk of pulmonary toxicity in patients treated with cytotoxic chemotherapy that includes cyclophosphamide and G-CSF or GMCSF.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Glyceraldehyde	L	An increase of the concentration of cytotoxic metabolites may occur with glyceraldehyde.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Indomethacin	L	Cyclophosphamide use concomitantly with indomethacin may cause severe pulmonary edema and acute life-threatening water intoxication.	Appropriate supportive measures should be employed if water intoxication occurs. Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Irraditation of the cardiac region	L	Increased cardiotoxicity may result from a combined effect of cyclophosphamide and irradiation of the cardiac region.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Lovastatin	L	Concurrent use in cardiac transplant patients of cyclophosphamide with the antihyperlipidemic HMG-CoA reductase inhibitor lovastatin may be associated with an increased risk of rhabdomyolysis and acute renal failure.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Methotrexate	L	Concurrent administration of methotrexate and cyclophosphamide may result in the inhibition of the metabolism of cyclophosphamide.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Metronidazole	L	Acute encephalopathy has been reported in a patient receiving cyclophosphamide and	Causal association is unclear. In an animal study, the combination of cyclophosphamide with metronidazole was associated with increased

Name / Class / Category	Ref	Effect	Clinical Comment
		metronidazole.	cyclophosphamide toxicity. Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Natalizumab	L	Increased hematotoxicity and / or immunosuppression may result from a combined effect of cyclophosphamide and natalizumab.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Ondansetron	L	There have been reports of a pharmacokinetic interaction between ondansetron and high-dose cyclophosphamide resulting in decreased cyclophosphamide AUC.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Paclitaxel	L	Increased hematotoxicity and / or immunosuppression may result from a combined effect of cyclophosphamide and paclitaxel. Increased hematotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Pentostatin	L	Increased cardiotoxicity may result from a combined effect of cyclophosphamide and pentostatin.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Phenobarbitone	L	Concomitant use of cyclophosphamide and phenobarbitone resulted in cyclophosphamide half-life decreased from 4.3 hours to 1.6 hours. In another study, cyclophosphamide biotransformation was increased 2 to 3 fold after phenobarbitone. In these studies, urinary excretion of metabolites over 48 hours was unchanged.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.

Name / Class / Category	Ref	Effect	Clinical Comment
Prednisone	L	Cyclophosphamide use concomitantly with prednisone may cause a fatal acute respiratory failure.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Protease Inhibitors	L	Concomitant use of protease inhibitors may increase the concentration of cytotoxic metabolites. Increased incidence of mucositis.	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 (NNRTI)-based regimen. Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Sulfonyl ureas	L	The blood glucose-lowering effect of sulfonyl ureas may be intensified when administered concomitantly with cyclophosphamide.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Tamoxifen	L	Concomitant use of tamoxifen and chemotherapy (including cyclophosphamide) may increase the risk of thromboembolic complications.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Thiazide diuretics (e.g. hydrochlorothiazide)	L	Increased hematotoxicity and / or immunosuppression may result from a combined effect of cyclophosphamide and thiazide diuretics.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Trastuzumab	L	Increased cardiotoxicity may result from a combined effect of cyclophosphamide and trastuzumab.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Vaccines	L	The immunosuppressive effects of cyclophosphamide can be expected to reduce the response to vaccination. Use of live vaccines may lead to vaccine-induced infection.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.

Name / Class / Category	Ref	Effect	Clinical Comment
Verapamil	L	Cytotoxic treatment has been reported to impair intestinal absorption of orally administered verapamil	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.
Zidovudine	L	Increased hematotoxicity and / or immunosuppression may result from a combined effect of cyclophosphamide and zidovudine.	Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention.

* This list provides some representative examples and is not an exhaustive list.
Legend: L = Literature

9.5 Drug-Food Interactions

Concomitant administration of grapefruit or grapefruit juice is not recommended since grapefruit contains a compound that may impair the activation of cyclophosphamide, and thereby its efficacy.

9.6 Drug-Herb Interactions

Inducers of human hepatic and extrahepatic microsomal enzymes (e.g., cytochrome P450 enzymes): The potential for increased formation of metabolites responsible for cytotoxicity and other toxicities (depending on the enzymes induced) must be considered in case of prior or concomitant treatment with, for example:

- St. John's wort

9.7 Drug-Laboratory Test Interactions

The following laboratory alterations have been reported in the literature and are potentially clinically significant:

Positive reactions may be suppressed:

- Candida skin test
- Mumps skin test
- Trichophyton skin test
- Tuberculin PPD skin test

False-positive results may be produced:

- Papanicolaou (PAP) test

Serum concentrations may be decreased:

- Pseudocholinesterase

Blood and urine concentrations may be increased:

- Uric acid

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Cyclophosphamide, a nitrogen mustard derivative, is a polyfunctional alkylating agent. The parent drug is inactive *in vitro*, when tested on cultures of human leukocytes or carcinomatous cells of human origin. The active metabolite of cyclophosphamide, phosphoramide mustard, exhibits the alkylating action. Phosphoramide mustard is formed, following the biological transformation through oxidation by hepatic microsomal enzymes under spontaneous ß-elimination of acrolein from aldophosphamide. The cytotoxic action of the active metabolite is primarily due to crosslinking of DNA and RNA strands, as well as inhibition of DNA synthesis. Cyclophosphamide is a potent immunosuppressive agent that also causes marked and persistent inhibition of cholinesterase activity. Alkylating metabolites of cyclophosphamide have been measured in cerebrospinal fluid, but, only a small fraction crosses the brain barrier.

10.3 Pharmacokinetics

Absorption

Cyclophosphamide is well absorbed from parenteral sites.

Bioavailability: The systemic availability, estimated from the ratio of areas under serum- concentration-time curves following oral and intravenous cyclophosphamide, was reported as 97% for a 100 mg, and 74% for a 300 mg dose.

In all the pharmacokinetic measurements in man, large inter-individual variations must be considered

Distribution

A mean apparent volume of distribution of cyclophosphamide was 0.56 L/Kg in adults and 0.67 L/Kg in children.

Tissue Distribution of cyclophosphamide after i.v. administration to cancer patients indicated that both unchanged parent drug and metabolites in small quantities penetrate the blood brain barrier; brain tissue concentrations being similar to those in blood. Biopsies, performed 2 hours after cyclophosphamide infusion, indicated approximately 30% more radioactivity in lymph nodes compared to muscle, adipose tissue or skin, but relative proportions of unchanged drug metabolites were not established.

Protein Binding: 12 to 14% of unchanged cyclophosphamide is protein-bound; the alkylating metabolites, however, are more extensively bound, namely 67% of the total plasma alkylating activity, and in another study, 39% of phosphamide mustard was protein-bound.

Metabolism

Cyclophosphamide is activated in liver to the active metabolite 4 hydroxy cyclophosphamide through phase I metabolism by cytochrome P450 (CYP) enzymes, including CYP2A6, 2B6, 2C8, 2C9, 2C19, 3A4 and 3A5. Detoxification is primarily

through glutathione S transferases (GSTA1, GSTP1) and alcohol dehydrogenase (ALDH1, ALDH3).

While chemically not reactive, the primary metabolites 4- hydroxycyclophosphamide and aldophosphamide are cytotoxic *in vitro*, and may represent transport forms of the alkylating moiety, phosphoramide mustard. The two primary metabolites can be further oxidized into the major urinary metabolites 5-ketocyclophosphamide and carboxyphosphamide. Nor-nitrogen mustard, a decomposition product of carboxyphosphamide, is an active alkylating agent with cytotoxicity *in vivo* and *in vitro*, however, little antitumour activity could be demonstrated; yet, it may play a role in the hematopoietic and other toxicities of cyclophosphamide. Another metabolite formed from aldophosphamide is acrolein, which has been identified as the most urotoxic species.

Disposition Kinetics: The decline in cyclophosphamide plasma levels following an i.v. dose is biexponential with terminal half-life averaging 7 hours (1.8 to 12.4) for adults, and 4 hours (2.4 to 6.5) for children; daily administration of approximately 50 mg/Kg bid or qid (i.v. infusion) to children significantly decreased both plasma half life and urinary excretion of cyclophosphamide. With daily exposure or repeated high-dose administration (i.v.) of cyclophosphamide to adult patients, the half-life of cyclophosphamide decreased without an increase in urinary excretion, suggesting that the drug induces its own metabolism. After an i.v. dose, the NBP [4-(nitrobenzyl)-pyridine] plasma alkylating activity peaks 2 hours after administration, and declines with a half-life of 7.7 hours. Phosphoramide mustard in 3 patients, receiving 60-75 mg/Kg cyclophosphamide, peaked 2 to 3 hours after the administration of cyclophosphamide at levels 10 to 20% of the unchanged drug, and declined slowly with levels still detectable at 24 hours.

Even with doses as high as 80 mg/Kg, the plasma half-life of cyclophosphamide does not increase.

The t½ and AUC of cyclophosphamide after a 5-day continuous infusion schedule of 300-400 mg/m^2/day, were similar to the t½ and AUC of a 1500 mg/m^2 i.v. bolus. The AUC of the alkylating activity after 5-day i.v. infusion, however, was three times higher than the AUC of alkylating activity after 1500 mg/m^2 i.v. bolus administration of cyclophosphamide. After cyclophosphamide administration to man and laboratory animals, significant differences in the pharmacokinetic parameters of the active metabolite 4-hydroxycyclophosphamide in both man and animals were found. In man, the active metabolite in blood was found at only low but longer lasting concentrations compared to the high and relatively short time concentration in blood of mice and rats, after a comparable dose.

Elimination

In man, a generally higher proportion of the administered cyclophosphamide is excreted as metabolites in urine. Urinary recovery of radioactivity after intravenously administered ^{14}C-cyclophosphamide to patients ranged from 59 to 82% after 4 days,

while not more than 20% of i.v. cyclophosphamide was excreted unchanged in urine at any dose level.

Renal clearance estimates of between 5.3 and 11 mL/min indicate substantial renal tubular reabsorption.

Special Populations and Conditions

- **Hepatic Insufficiency:** A patient with Hodgkin's disease showing jaundice, markedly elevated alkaline phosphatase and filling defects on liver scan had the longest cyclophosphamide half life (8.4 hrs) and lowest peak plasma alkylating metabolite level (4.2 µmoles/mL) of 12 patients having received 40 mg/Kg cyclophosphamide. Prior hepatic dysfunction and / or hepatotoxic medication might predispose the patient to oral cyclophosphamide toxicity by altering the balance between the enzymatic production of non-toxic metabolites (carboxyphosphamide) and the decomposition of aldophosphamide to the effective alkylating agent phosphoramide mustard.

- **Renal Insufficiency:** Patients with severe renal function impairment have a normal biotransformation of cyclophosphamide, but impaired excretion of metabolites with significantly higher plasma alkylating activity. Dose modification of cyclophosphamide, related to the degree of renal dysfunction, may be advised. Patients with moderate to severe renal impairment receiving high doses of cyclophosphamide or those with severe renal impairment receiving conventional doses may require dose reduction, e.g., a dose reduction of 50% for a glomerular filtration rate below 10 mL/minute is recommended.

  Cyclophosphamide is dialysable with a high extraction efficiency.

11 STORAGE, STABILITY AND DISPOSAL

Store vials at 2°C to 8°C. The vials must be refrigerated.

Stability of Solutions

Storage:

If not used immediately, cyclophosphamide solutions should be stored as described in the following table.

Table 5: Storage of Cyclophosphamide Solutions

Diluent	Storage	
	Room Temperature (15°C to 25°C)	Refrigerated (2°C to 8°C)
Diluted Solution for Direct Intravenous Injection		
0.9% Sodium Chloride Injection, USP	up to 24 hrs	Up to 3 days

Diluent	Storage	
	Room Temperature (15°C to 25°C)	Refrigerated (2°C to 8°C)
Diluted Solutions for Intravenous Infusion		
0.9% Sodium Chloride Injection, USP	up to 24 hrs	up to 3 days
5% Dextrose Injection, USP	up to 24 hrs	up to 36 hrs
5% Dextrose and 0.9% Sodium Chloride Injection, USP	up to 24 hrs	up to 36 hrs

Unless prepared under aseptic conditions, reconstituted solutions should be used within 8 hours after dilution.

12 SPECIAL HANDLING INSTRUCTIONS

Handling and Disposal

Cyclophosphamide for Injection is cytotoxic, carcinogenic, mutagenic and teratogenic. Avoid ingestion, inhalation, or skin and eye contact. Mandatory washing of hands before and after using gloves must be advised. If necessary, consult the Company's **M**aterial **S**afety **D**ata **S**heet.

Personnel, regularly handling these agents should have frequent hematologic examinations (CBC), and frequently be screened for urine mutagenesis.

Work-practice guidelines for personnel dealing with and handling cytotoxic and hazardous preparations must be respected, to minimize unnecessary exposure to cyclophosphamide in physicians, nurses, pharmacists, and technicians.

Appropriate Personal Protective Equipment (PPE) must be available in all areas where cyclophosphamide is handled. See the following table:

Table 6: Handling and Disposal of Personal Protective Equipment (PPE)

Activity (When to Wear)	Personal Protective Equipment (PPE)			
	Gloves:	**Gown:**	**Eye Protection:**	**Mask**:
	Surgical Latex (7-9 mil thickness) or material which provides equal or better protection. Gloves must be changed at least hourly or immediately if contaminated, torn or punctured. Wash hands with soap and water after removal of gloves	Moisture-resistant, long-sleeved gown with cuffs. Gowns must be changed daily, immediately if contaminated and immediately after spill clean-up.	Eye / face protection (e.g., chemical splash goggles) must be worn when there is hazard of eye contact.	(As approved by Workers Compensation Board)

Activity (When to Wear)	Personal Protective Equipment (PPE)			
	Gloves:	**Gown:**	**Eye Protection:**	**Mask**:
Preparation	Always	Always	If preparing outside a biological safety cabinet	No
Administration	Always	Always	If hazard of eye contact	No
Spill Clean-up	Always	Always	Always	Yes
Waste Disposal	Always	If waste uncontained	If waste uncontained	No

Preparation of Cyclophosphamide for Injection must take place in a Pharmacy or, in facilities where there is not a Pharmacy, in a Class II Type B or better, externally-vented biological safety cabinet. The biological safety cabinet should have airflow monitoring devices and should be certified at least annually. Only luer-lock connections should be used in the preparation of Cyclophosphamide for Injection.

Disposal of **cyclophosphamide**-contaminated clothing, gloves, utensils, broken glass etc. must be considered as hazardous waste. It must be deposited into a 4 mil thick polypropylene hospital trash bag (properly labelled), or be otherwise segregated and incinerated at above 1000°C. Chemical inactivation should, if possible, be avoided, since it is often ineffective and may produce byproducts that are more mutagenic than the parent drug.

Spills: Cleaning up immediately and decontaminating areas of spills and breakage by experienced and well-protected personnel is of utmost importance. Contaminated areas including hood interiors must have clearly worded warning labels posted. It is suggested that spill kits be easily accessible, and include replacement hood filters, a respirator (“P3" filter, Manufacturer's current recommendation for cyclophosphamide powder spills), chemical splash goggles, at least 2 pairs of protective gloves, at least 2 sheets (31cm x 33cm/12" x 13") of absorbent material, 250 mL and 1 Liter spill-control pillows, a small scoop, spatula, forceps or tweezers to collect glass fragments, and at least two large polypropylene hospital trash bags 4 mil or thicker, or other cytotoxic drug waste-disposal bags, puncture- and leak-resistant waste container for sharp or breakable objects or spilled liquid, and warning sign (e.g., “ Danger - Cytotoxic Agent Spill”). Absorbents should be incinerable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

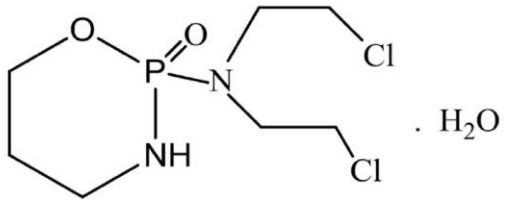
Drug Substance

Proper name: Cyclophosphamide Monohydrate, Ph.Eur

Chemical name: (2RS)-N,N-bis(2-chloroethyl)tetrahydro-2H-1,3,2-Oxazaphosphorin-2-amine-2-oxide monohydrate

Molecular formula and molecular mass: $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$ and 279.1 g / mol

Structural formula:



Physicochemical properties:

Physical Form: A white or almost white crystalline powder.

Solubility: Soluble in water and freely soluble in alcohol

pH Values: Between 4 and 6

14 CLINICAL TRIALS

Not Applicable

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicity:

Acute Toxicity

The following lethality studies were undertaken in male and female CDF_1 mice, using single or multiple **i.v.** cyclophosphamide dose regimen.

SINGLE DOSE	MALE	FEMALE
LD_{90}	828.01 mg/Kg	652.92 mg/Kg
LD_{50}	524.46 mg/Kg	416.99 mg/Kg
LD_{10}	332.19 mg/Kg	265.10 mg/Kg
SINGLE DOSE x 5	**MALE**	**FEMALE**
LD_{90}	191.69 mg/Kg	131.30 mg/Kg
LD_{50}	145.49 mg/Kg	79.37 mg/Kg
LD_{10}	110.43 mg/Kg	47.98 mg/Kg

Intravenous LD_{50} was reported as 40 mg/Kg for dogs, 130 mg/Kg for rabbits, 160 mg/Kg for rats, and 400 mg/Kg for guinea pigs.

Oral LD_{50} for cyclophosphamide in mice after:		in rats after:
24 h	780 mg / Kg	---
48 h	750 mg / Kg	720 mg / Kg
120 h	600-726 mg / Kg	235 mg / Kg
7 days	580 mg / Kg	142 mg / Kg
14 days	350 mg / Kg	94 mg / Kg

The 14-day LD_{50} for oral cyclophosphamide in dogs was reported as 44 mg/Kg.

Subcutaneous 100 mg/Kg chloramphenicol prior to 300 mg/Kg or 200 mg/Kg i.p. cyclophosphamide in adult rats is capable of partially protecting against the toxic and lethal effects of cyclophosphamide.

The efficacy of 50 mg/Kg i.p. cyclophosphamide in 150 to 200 newborn and adult Swiss male mice per experiment under depleted and supplemented condition of vitamin **A** (p.o. 100 and 250 IU/mouse/day) was scrutinized. Supplemental vitamin **A** helped to check progression of solid murine sarcoma 180 growth, and also increased the effectiveness of chemotherapy.

Cyclophosphamide titration in mice appears to enhance survival following treatment with cyclophosphamide up to, but not exceeding 450 mg/Kg. Hematuria was very much lower in the titrated group, also lung damage was less in the titrated mice.

Intraperitoneal injection of cyclophosphamide, acrolein and phosphamide mustard into mice was used, to determine, which of the metabolites is responsible for ovarian toxicity. Using follicle destruction, ovarian volume and uterine weight as toxicity parameters, the investigators found only phosphoramide mustard responsible for cyclophosphamide ovarian toxicity.

Chronic Toxicity

Studies, using rats that received up to 12 mg/Kg cyclophosphamide by stomach tube for 80 days, indicated that the highest dose produced a 75% mortality rate after 8 weeks. Leukopenia was observed in all animals after 4 weeks of treatment. A high incidence of hematuria and petechial hemorrhage was found in lungs, gastrointestinal tract and urinary bladder.

Dogs receiving cyclophosphamide p.o. of up to 5 mg/Kg 5 days a week for 6 weeks, presented a reduction in body weight, leukopenia and limited hemorrhagic lesions in lymph nodes, bladder, brain, lung, gastrointestinal tract and renal pelvis. Severity of bone marrow changes was related to dosage.

Chronic administration of toxic doses led to hepatic lesions manifested as fatty degeneration followed by necrosis. The intestinal mucosa was not affected. The threshold for hepatotoxic effects was 100 mg/Kg in the rabbit and 10 mg/Kg in the dog.

Carcinogenicity: The carcinogenic effect of cyclophosphamide have been demonstrated in animal studies on rats and mice.

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

Reproductive and Developmental Toxicology: Reproductive and teratologic toxicity of cyclophosphamide in animals is well documented. Animal data indicate that exposure of oocytes during follicular development may result in a decreased rate of implantations and viable pregnancies, and in an increased risk of malformations.

17 SUPPRORTING PRODUCT MONOGRAPH

1. Pr PROCYTOX® (cyclophosphamide) tablets 25 mg, 50 mg and powder for injection 200 mg, 500 mg, 1000 mg, 2000 mg per vial, submission control number 155509, Product Monograph, Baxter Corporation. 2012-09-07.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrCyclophosphamide for Injection

Read this carefully before you start taking **Cyclophosphamide for Injection** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Cyclophosphamide for Injection.**

Serious Warnings and Precautions

- cyclophosphamide is a potent cancer medicine, administered only by trained healthcare professionals
- you will have regular blood, liver, and kidney tests while receiving this medicine.
- even a single dose may:
  - harm your heart
  - damage your lung
- cyclophosphamide may:
  - increase your risk of getting other cancers.
  - lead to serious heart rhythm problems (QT prolongation and arrhythmia)
  - damage your liver
  - severely lower your blood cell counts. This can lower your body's ability to fight infections. This is called myelosuppression. While receiving this medicine:
    - check your temperature often, especially if you feel unwell
    - call your healthcare professional right away if you get a fever or feel signs of an infection (like chills, sore throat, or feeling very tired)
  - harm your bladder and kidneys. If your urine (pee) turns pink or red, tell your healthcare professional right away. To prevent bladder problems, drink lots of water or other liquids
  - cause life-threatening allergic reactions
  - interact with certain medications called muscle relaxants
- certain type of vaccines (live vaccines) may cause infection in people receiving cyclophosphamide
- Cyclophosphamide for Injection contains alcohol. Talk to your healthcare professional before receiving this medicine

For more information on the serious side effects of cyclophosphamide, see the **Serious side effects and what to do about them** table, below.

What is Cyclophosphamide for Injection used for:

Cyclophosphamide for Injection is used alone or with other medications to treat the following type of cancer:
- lymphomas
- multiple myeloma
- leukemias
- mycosis fungoides

- neuroblastoma
- breast cancer
- retinoblastoma
- lung cancer

How does Cyclophosphamide for Injection work?

Cyclophosphamide is a cancer-fighting medicine. It belongs to a group of medicines called antineoplastics, and more specifically, to a class known as alkylating agents.

- it works by damaging the DNA of cancer cells, which slows or stops their growth and helps prevent the cancer from spreading
- because it also affects some healthy cells, it can cause side effects like hair loss, nausea, or low blood cell counts

What are the ingredients in Cyclophosphamide for Injection?

Medicinal ingredient: Cyclophosphamide

Nonmedicinal ingredients: ethanol anhydrous.

Cyclophosphamide for Injection comes in the following dosage forms:
Cyclophosphamide for Injection is available as a sterile solution in single-use vials with the following strengths:

- 500 mg / mL
- 1 g in 2 mL
- 2 g in 4 mL

Do not receive Cyclophosphamide for Injection if:

- you are allergic to this medicine, its ingredients, or anything used to make or store it.
- you have trouble passing urine (urinary blockage) or bladder infection
- you have very low blood cell counts (severe bone marrow suppression)
- you have serious kidney or liver problems
- you have a serious infection, especially chickenpox or shingles (varicella zoster).
- your immune system is severely weakened
- you are under 18 years old
- you are pregnant
- you are breastfeeding
- you are of Asian descent and have a specific genetic condition called ALDH2 mutation

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Cyclophosphamide for Injection. Talk about any health conditions or problems you may have, including if you:

- have any of the following conditions:
  - a heart condition called QT prolongation or a family history of it.
  - electrolyte imbalances (problems with minerals like sodium in your blood).
  - cancer that has spread to the brain or bone marrow

  - low blood cell levels (low white blood cells, platelets, or red blood cells)
  - liver or kidney problems
  - trouble urinating or a bladder infection
  - an active infection
  - high serum creatinine levels (a waste product made by your muscles and remove through urine)
- have had surgery in the last 10 days or have upcoming surgery (including dental surgery), as cyclophosphamide can slow wound healing
- have received in the past a common cancer treatment known as radiation therapy
- are scheduled to receive a vaccine
- you are caring for a child under 18 years old (cyclophosphamide is not recommended for children under 18)

Other warnings you should know about:

- **Pregnancy, Breastfeeding, and Fertility**

  If you are a **woman**:
  - **Pregnancy:** This medicine can harm an unborn baby
    - **do not** receive cyclophosphamide if you are pregnant or planning to become pregnant
    - if you become pregnant while taking cyclophosphamide tell your healthcare professional right away, to discuss the best options for you and your baby
    - use effective birth control during treatment and for at least **12 months** after the last dose
    - talk to your healthcare professional about safe birth control options
  - **Breastfeeding:**
    - **do not** breastfeed while receiving cyclophosphamide
    - the medicine can pass into breast milk and harm your baby

  If you are a **man:**
  - if you are planning to father a child, talk to your healthcare professional before starting treatment
  - if your partner is pregnant or may become pregnant, use effective birth control during treatment and for at **least 6 months** after your last dose

  For both **men** and **women**:
  - **Fertility:**
    - cyclophosphamide may affect your ability to have children in the future.
    - if you are planning to have children later on, talk to your healthcare professional before starting treatment

- **Driving and using machines after your treatment:**
  - this medicine may make you feel dizzy, nauseous, less alert, or affect your balance and vision
  - for **1 to 2 hours** after your treatment, **do not drive**, use heavy machines, or do anything that needs your full attention
  - **avoid alcohol** while taking this medicine. It can make side effects like nausea

and vomiting worse and may reduce how well the medicine works

- **Alcohol in this medication**
  - this medication (Cyclophosphamide for Injection) contains alcohol, which can affect your brain and nervous system, especially right after treatment.
  - if you need to avoid alcohol for medical or other reasons, talk to your healthcare professional before using this medicine

- **Blood tests and monitoring:** While you are taking cyclophosphamide, your healthcare team will do regular tests to make sure your body is handling the medicine safely. These may include:
  - blood tests – to check your white blood cells, platelets, and red blood cells
  - urine tests – to look for signs of bladder irritation or damage
  - liver tests – to monitor how well your liver is working
  - electrolyte tests – to check levels of essentials minerals like sodium and potassium
  - lung tests – because this medicine can affect your lungs
  - heart tests – to check your heart rhythm and function

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Cyclophosphamide for Injection:

- alcohol – can increase side effects like nausea and vomiting
- antibiotics – such as ciprofloxacin, metronidazole, rifampin, chloramphenicol, and sulfonamides
- blood thinners – like warfarin (Coumadin)
- antidepressants medicines – such as St. John's wort and bupropion
- antifungal medications – like fluconazole and itraconazole
- stomach acid reducers – like cimetidine
- corticosteroids medicines – such as prednisone
- medications for alcohol use disorders – like disulfiram
- rheumatoid arthritis medicines – including etanercept and indomethacin.
- cholesterol medications – such as lovastatin
- gout medicines – like allopurinol
- seizure medications – such as phenytoin, carbamazepine, and phenobarbital
- blood pressure medicines – like ACE inhibitors and water pills (thiazide diuretics, e.g., hydrochlorothiazide)
- heart medicines – including amiodarone, digoxin, prasugrel, and verapamil.
- antinausea medications – like aprepitant and ondansetron
- medications that boost bone marrow – such as G-CSF and GM-CSF.
- other cancer treatments – including busulfan and tamoxifen
- medicines that affect the immune system – like cyclosporine, azathioprine, and methotrexate
- sedatives – medicines to help you feel calm, relaxed, or sleepy like chloral hydrate and benzodiazepines
- diabetes medicines – like sulfonylureas
- HIV medicines – such as protease inhibitors and zidovudine.
- vaccines – especially live vaccines (these can cause infection in people with weakened immune systems)

- grapefruit:
  - **do not eat** grapefruit or drink grapefruit juice while taking this medication.
  - grapefruit contains a compound that can interfere with how cyclophosphamide works
  - this may make the medicine less effective in treating your condition
- radiation – use to treat cancer: If you have had radiation to your chest or heart, let your healthcare professional know

How to receive Cyclophosphamide for Injection:

- your healthcare professional will give you cyclophosphamide through a vein (by IV)
- your healthcare professional may want you to drink extra fluids so that you will pass more urine. This will help prevent kidney problems and keep your kidneys working well

Usual dose:

Your healthcare professional will:
- choose the right dose of Cyclophosphamide for Injection for you
- decide how often you should receive it

Overdose:

If you think you, or a person you are caring for, have taken too much Cyclophosphamide for Injection, contact a health care professional, hospital emergency department or regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:
If you miss a scheduled treatment, talk to your healthcare team as soon as possible to find out what to do.

What are possible side effects from using Cyclophosphamide for Injection
These are not all the possible side effects you may have when taking Cyclophosphamide for Injection. If you experience any side effects not listed here, tell your healthcare professional.

Cyclophosphamide for Injection may cause side effects. Tell your healthcare professional if any of these symptoms are severe or do not go away:
- nausea, vomiting, diarrhea, weight loss, or stomach pain
- loss of appetite or weight
- fatigue (tiredness)
- hair loss (in most cases, grow back after treatment, but the texture or color may change).
- sores on the mouth or tongue
- changes in skin color
- changes in color or growth of finger or toe nails

Serious side effects and what to do about them			
Frequency / Side Effect / Symptom	**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Myelosuppression (severely low blood cell counts) ○ **Anemia** (low level of red blood cells): fatigue, pale skin, headache, shortness of breath, dizziness, weakness, difficulty sleeping). ○ **Neutropenia** (Low Levels of white blood cells): watch out for signs of infection (feeling unwell, feeling hot (like you have a fever), chills or shaking, flu-like feeling, sore throat or sores in your mouth with a fever, diarrhea (watery stool (poo)) with a fever, cough with thick and sticky yellow or green fluid) ○ **Thrombocytopenia** (low levels of platelets): easy bruising, unusual nosebleeds or bleeding from the gums, small, scattered spots on your skin that are red, pink, or purple		√	
Central Nervous System problems (problems that affect how your brain and spinal cord work): dizziness, confusion, convulsions, headache)		√	
Acute pancreatitis (inflammation of the pancreas, an organ that lies in the back of the mid-abdomen)**:** sudden and severe pain in the upper belly that may spread to the back, fever, swollen or tender abdomen			√
Rhabdomyolysis (muscle breaks down): severe muscle pain or weakness, dark-colored pee			√
Liver problems: yellowish skin or eyes, unusually dark pee or pain on the right side of your belly			√
Lung problems: new or worsening cough, burning sensation in the chest, shortness of breath, chest discomfort, trouble breathing during usual daily activities			√
Kidney and Urinary problems (Irritation of the bladder wall): pink or red colored urine (pee), blood in your pee; feel the need to pee urgently, have pain in your belly / lower belly area or pain when peeing		√	

Serious side effects and what to do about them			
Frequency / Side Effect / Symptom	**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
	Only if severe	**In all cases**	
Phlebitis (inflammation of vein): pain, hardening, and swelling of a vein in your arms or legs		√	
UNCOMMON			
Heart problems: chest pain, fainting spells (passing out) or swelling in your legs, ankles and belly, new or worsening shortness of breath, a cough that does not go away, pounding or irregular heartbeat (palpitations), sudden weight gain (more than 5 pounds in 24 hours)			√
Hypotension (low blood pressure): dizziness, fainting, light-headedness.		√	
Peripheral neuropathy: prickling, tingling, or numbness in the arms or legs		√	
Steven-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (Serious skin reactions): any combination of itchy skin rash, redness, blistering and peeling of the skin and / or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands, joint pain, yellowing of the skin or eyes, dark-coloured pee			√
Tumor lysis syndrome (occur when cancer cells break down rapidly, usually after starting cancer treatment): peeing less than usual, confusion, muscle twitching, seizures			√
Anaphylaxis (serious allergic reactions): swelling of your face, eyelids, lips, mouth, tongue, or throat; trouble breathing or throat tightness; or skin rash.			√
Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) (a condition where the body makes too much antidiuretic hormone (ADH)—a hormone that helps control water balance): concentrated and dark urine (pee), muscle cramps, confusion, seizures		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store vials in a refrigerator at 2°C to 8°C.
- **Do not use** the medicine if:
  - the liquid looks cloudy
  - you see particles in it
  - the color has changed
  - the vial is leaking

If you want more information about Cyclophosphamide for Injection:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.drreddys.com, or by calling 1-855-845-1739.

This leaflet was prepared by Dr. Reddy's Laboratories Ltd.

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