ENDOXAN
Cyclophosphamide Powder for Injection
500mg, 1.0g or 2.0g

NAME OF DRUG
ENDOXAN is available in 3 strengths: 500mg, 1.0g or 2.0g of cyclophosphamide per vial.

DESCRIPTION
Cyclophosphamide is chemically 2-Bis (2-chloroethyl) aminoperhydro-1, 3, 2-oxazaphosphorine 2-oxide. It exists as the monohydrate. The chemical formula is C₇H₁₅Cl₂N₂O₂P.H₂O and its molecular weight is 279.1. The CAS number is 6055-19-2 and the chemical structure is as follows:

The white crystalline monohydrate is soluble in water (>4% w/v). Cyclophosphamide monohydrate liquefies when its water of crystallisation is lost.

ACTIONS
Cytostatic alkylating agent

Pharmacology
Site and mode of action: Although it is classified generally as an alkylating agent, cyclophosphamide itself is not an alkylating agent or irritant. It appears to be inactive in vitro when tested on cultures of human leucocytes or carcinomatous cells of human origin.

However, cyclophosphamide is converted to its active form by microsomal enzymes in the liver, and interferes in vivo with the growth of susceptible neoplasms and, to a certain extent, with normal tissue regeneration. The cytotoxic action of cyclophosphamide evident in vivo is the basis for its therapeutic use as an antineoplastic agent and for some adverse reactions associated with its use.

Cyclophosphamide also has immunosuppressive properties.
Pharmacokinetics

Absorption: Cyclophosphamide is absorbed from the gastrointestinal tract and from parenteral sites. It appears to be absorbed also when it is applied topically to neoplastic tissues, situated on the surface of the body.

Distribution: The tissue distribution of cyclophosphamide has been examined in cancer patients following intravenous administration. It was found that both unchanged drug and metabolites pass the blood-brain barrier. Cerebral tissue contained radioactivity in a concentration range similar to that found in blood. Biopsies performed 2 hours after administration of the drug revealed that about 30% more radioactivity was present in lymph nodes than in muscle, adipose tissue, or skin, but the relative proportions of unchanged drug and metabolites was not established.

Metabolism: Cyclophosphamide is metabolised in the body initially by the mixed function oxidase enzymes of the liver microsomes; several toxic metabolites have been identified.

Peak plasma concentrations of metabolites have been found to be almost proportional to the administered dose, but relatively wide individual variations have been reported. Peak plasma alkylating metabolite levels generally are reached at 2-3 hours after administration of the drug reaching maximum values of only one-half to three-quarters of those obtained in rats given comparable doses. The average plasma alkylating metabolite concentrations at 8 hours after intravenous administration of the drug was about 77% of the peak level when studied in 12 patients without prior drug exposure.

There is much more variability in the rate of metabolism of cyclophosphamide among different human subjects than there is in nonhuman species. The plasma half-life of the unchanged drug is apparently independent of age, race, sensitivity, or resistance to the drug, diagnosis or dosage.

Excretion: In humans, a generally higher proportion of the administered dose is excreted in the urine as metabolites. Of three alkylating metabolites found in urine, only one (nor-nitrogen mustard) has been definitely identified. Recovery of radioactivity after intravenously administered labelled cyclophosphamide ranged from 37% to 82%, with 20% to 45% of that recovered attributable to the unchanged drug. The total urinary excretion of unchanged cyclophosphamide ranged from 3% to 30% of the dose with most cases in the upper half of the range.

Half-life: Intravenously administered cyclophosphamide is reported to have a serum half-life of between 6 and 8 hours in adults; however, the drug and/or its metabolites may be detected in plasma for up to 72 hours. The half-life in children is relatively shorter.
Protein binding: Cyclophosphamide does not bind to human plasma proteins in appreciable amounts but on single intravenous doses of a $^{14}$C-labelled cyclophosphamide, it results in $14\pm2.5\%$ and $12\pm5\%$ of total radioactivity being bound to plasma proteins at cyclophosphamide concentrations of 10 and 200 micromol/mL. The metabolites of cyclophosphamide are protein bound to a greater extent than the parent drug. Repeated doses increased the amount of radioactivity bound to plasma. Following five doses of 40mg/kg about 56% of the plasma radioactivity was bound.

INDICATIONS

The proper use of cyclophosphamide requires accurate diagnosis, careful assessment of the anatomic extent of the disease, knowledge of the type and effects of any previous therapy, and continued evaluation of the patient’s general and haematologic status. It is essential that adequate clinical and laboratory facilities be available for proper monitoring of patients during treatment with cyclophosphamide.

The clinical course of the disease should be recorded in objective terms before treatment is begun and thereafter at regular intervals. Careful management of patients receiving cyclophosphamide will help achieve maximum benefit with minimum risk.

Antineoplastic properties: Patients with neoplasms that might preferably be treated by surgical and/or irradiation procedures should ordinarily not be treated by chemotherapy alone.

The following classification is a guide to the various neoplastic conditions in which benefit may be derived from chemotherapy with cyclophosphamide.

Frequently responsive myeloproliferative and lymphoproliferative disorders.
Malignant lymphomas including Hodgkins (stages III and IV, Peter’s Staging System*) and non-Hodgkins lymphomas; multiple myeloma; leukaemias; mycosis fungoides (advanced disease).


Stage I: Disease limited to one anatomic region (Stage I) or two contiguous anatomic regions (Stage I$^2$) on the same side of the diaphragm.

Stage II: Disease in more than two anatomic regions or two contiguous regions on the same side of the diaphragm.

Stage III: Disease on both sides of the diaphragm, but not extending beyond the involvement of lymph nodes, spleen, and/or Waldeyer’s ring.

Stage IV: Involvement of the bone marrow, lung parenchyma, pleura, liver, bone, skin, kidneys, gastrointestinal tract, or in any tissue or organ in addition to lymph nodes, spleen or Waldeyer’s ring.
All stages are subclassified as A or B to indicate the absence or presence, respectively, of systemic symptoms.

*Frequently responsive solid malignancies:* Neuroblastoma (patients with disseminated disease); adenocarcinoma of the ovary, retinoblastoma.

*Infrequently responsive malignancies:* Carcinoma of the breast; malignant neoplasms of the lung.

**Immunosuppressive properties**

Cyclophosphamide has also been used in the treatment of autoimmune diseases and immunopathies of unspecified type (ie Wegener’s granulomatosis) when these diseases have been resistant to conventional first and second line of treatment, and for the prevention of transplant rejection. Cyclophosphamide can be recommended for use in treatment of nonmalignancies only when in the opinion of the physician the benefits to the patient outweigh the risk of treatment with cyclophosphamide.

**CONTRAINDICATIONS**

ENDOXAN should not be used in patients with:

- known hypersensitivity to cyclophosphamide, or any of its metabolites
- severely impaired bone marrow function (particularly in patients who have been pre-treated with cytotoxic agents and/or radiotherapy)
- inflammation of the bladder (cystitis)
- urinary outflow obstruction
- active infection

Cyclophosphamide therapy should not be commenced for 4 to 8 days after major surgery.

Patients of both sexes in the reproductive age should take contraceptives during therapy and for 3 months post-therapy. ENDOXAN should not be taken in the first trimester of pregnancy.

**WARNINGS**

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.

Treatment with cyclophosphamide may cause myelosuppression and significant suppression of immune responses.

Cyclophosphamide-induced myelosuppression can cause leukopenia, neutropenia, thrombocytopenia (associated with a higher risk of bleeding events), and anaemia.
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. Infections must be treated appropriately.

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 antifungals must be given.

Cyclophosphamide should be used with caution, if at all, in patients with severe impairment of bone marrow function and in patients with severe immunosuppression.

Unless essential, cyclophosphamide should not be administered to patients with a leukocyte count below 2500 cells/microliter (cells/mm³) and/or a platelet count below 50,000 cells/microliter (cells/mm³).

Cyclophosphamide treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop a serious infection.

In principle, 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 bone marrow recovers relatively quickly, and the levels of peripheral blood cell counts normalize, as a rule, after approximately 20 days.

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

Close haematological monitoring is required for all patients during treatment.
- Leukocyte counts must be obtained prior to each administration and regularly during treatment (at intervals of 5 to 7 days when starting treatment, and every 2 days if the counts drop below 3000 cells/microliter (cells/mm³)).
- Platelet count and haemoglobin value should be obtained prior to each administration and at appropriate intervals after administration.

**Urinary Tract and Renal Toxicity**
Haemorrhagic cystitis, pyelitis, ureteritis, and haematuria have been reported with cyclophosphamide therapy. Bladder ulceration/necrosis, fibrosis/contracture and secondary cancer may develop.

Urotoxicity may mandate interruption 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. Haemorrhagic cystitis after single doses of cyclophosphamide has been reported. Past or concomitant radiation or busulfan treatment may increase the risk for cyclophosphamide-induced haemorrhagic cystitis. Cystitis is, in general, initially abacterial. Secondary bacterial colonization may follow.

Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions. Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity. Cyclophosphamide should be used with caution, if at all, in patients with active urinary tract infections.

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

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

Cardiotoxicity, Use in Patients with Cardiac Disease
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 haemorrhagic myocarditis. Hemopericardium has occurred secondary to haemorrhagic myocarditis and myocardial necrosis.

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 for example, 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.

Pulmonary Toxicity
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. While the incidence of cyclophosphamide-associated pulmonary toxicity is low, 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.

Secondary Malignancies
As with all cytotoxic therapy, treatment with cyclophosphamide involves the risk of secondary tumours and their precursors as late sequelae.

The risk of urinary tract cancer as well as the risk of myelodysplastic alterations, partly progressing to acute leukaemias, 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.

The risk of bladder cancer can be markedly reduced by prevention of haemorrhagic cystitis.

Genotoxicity
Cyclophosphamide is genotoxic and mutagenic, both in somatic and in male and female germ cells. Therefore, women should not become pregnant and men should not father a child during therapy with cyclophosphamide.

Men should not father a child for up to 6 months after the end of therapy.

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.

Sexually active women and men should use effective methods of contraception during these periods of time.

Effects on Fertility
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 during prepubescence generally develop secondary sexual characteristics normally and have regular menses.

Girls treated with cyclophosphamide during prepubescence subsequently have conceived.

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.

Sexual potency and libido generally are unimpaired in these patients.

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.

Men temporarily rendered sterile by cyclophosphamide have subsequently fathered children.

**Anaphylactic Reactions, Cross-sensitivity with Other Alkylating Agents**

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

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

**Mutagenic Potential:** Patients, male or female, capable of conception should be advised of the mutagenic potential of cyclophosphamide. Adequate methods of contraception appear desirable for such patients receiving cyclophosphamide.

**Oncogenic potential and secondary neoplasia:** Cyclophosphamide has been reported to have oncogenic activity in rats and mice. The possibility that it may have oncogenic potential in humans undergoing long-term immunosuppressive therapy should be considered.
Secondary malignancies have developed in some patients treated with cyclophosphamide alone or in association with other antineoplastic drug and/or modalities. These malignancies have more frequently been urinary bladder, myeloproliferative, and lymphoproliferative malignancies. Secondary malignancies more frequently develop in cyclophosphamide-treated patients with primary myeloproliferative disease in which immune processes are believed to be pathologically involved. In some cases, the secondary malignancy was detected up to several years after cyclophosphamide treatment was discontinued. The secondary urinary bladder malignancies have generally occurred in patients who previously developed haemorrhagic cystitis (see Warnings, Haemorrhagic cystitis). Although no cause-effect relationship has been established between cyclophosphamide and the development of malignancy in humans, the possibility of secondary malignancy, based on available data, should be considered in any benefit-to-risk assessment for the use of the drug.

Adrenalectomised patients: Since cyclophosphamide has been reported to be more toxic in adrenalectomised dogs, adjustment of the doses of both replacement steroids and cyclophosphamide may be necessary for the adrenalectomised patient.

Haemorrhagic cystitis: Sterile haemorrhagic cystitis can result from the administration of cyclophosphamide. This can be severe, even fatal, and is probably due to metabolites in the urine. Nonhaemorrhagic cystitis and/or fibrosis of the bladder have also been reported to result from cyclophosphamide administration. Atypical epithelial cells may be found in the urinary sediment. Ample fluid intake and frequent voiding help to prevent the development of cystitis, but when it occurs, it is necessary to interrupt cyclophosphamide therapy.

Haematuria usually resolves spontaneously within a few days after cyclophosphamide therapy is discontinued, but may persist for several months. In severe cases replacement of blood loss may be required. The application of electrocautery to telangiectatic areas of the bladder and diversion of urine flow have been successful methods used in the treatment of protracted cases. Cryosurgery has also been used. (See also Warnings, Secondary neoplasia). Nephrotoxicity including haemorrhage and clot formation in the renal pelvis have been reported.

The above bladder toxicity can be prevented in many cases by concurrent use of the uroprotector UROMITEXAN (mesna). 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. Please consult the product information for UROMITEXAN for more information.

Pulmonary fibrosis: Interstitial pulmonary fibrosis has been reported in patients receiving high doses of cyclophosphamide over a prolonged period.

Secondary infection: Because cyclophosphamide may exert a suppressive action in immune mechanisms, the interruption or modification of dosage should be considered for patients who develop bacterial, fungal or viral infections. This is especially true for patients receiving concomitant steroid therapy, since infections appear to be particularly dangerous under these circumstances.
Use in pregnancy (Category D)
Cyclophosphamide can be teratogenic or cause foetal resorption in experimental animals. It should not be used in pregnancy, particularly in early pregnancy unless, in the judgement of the physician, the potential benefits outweigh the possible risks.

Cyclophosphamide crosses the placental barrier. Treatment with cyclophosphamide has a genotoxic effect and may cause foetal damage when administered to pregnant women.

Malformations have been reported in children born to mothers treated with cyclophosphamide during the first trimester of pregnancy. However, there are also reports of children without malformations born to women exposed during the first trimester.

Exposure to cyclophosphamide in utero may cause miscarriage, foetal growth retardation, and fetotoxic effects manifesting in the newborn, including leukopenia, anaemia, 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 as long as oocytes/follicles exist that were exposed to cyclophosphamide during any of their maturation phases.

If cyclophosphamide is used during pregnancy, or if the patient becomes pregnant while taking this drug or after treatment, the patient should be apprised of the potential hazard to a foetus.

Use in lactation
Cyclophosphamide is excreted in breast milk. Breastfeeding should be terminated prior to institution of cyclophosphamide therapy.

Neutropenia, thrombocytopenia, low haemoglobin, and diarrhoea have been reported in children breast fed by women treated with cyclophosphamide. Women must not breastfeed during treatment with cyclophosphamide.

Use in the elderly
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.
PRECAUTIONS

Cyclophosphamide should be given cautiously to patients with any of the following conditions:

Leucopenia
Thrombocytopenia
Tumour cell infiltration of bone marrow
Previous X-ray therapy
Previous radiotherapy
Previous therapy with other cytotoxic agents
Impaired hepatic function
Impaired renal function
Weakened or elderly patients

Patients with a weakened immune system, e.g., those with diabetes mellitus, also require close observation.

Before starting treatment, it is necessary to exclude or correct any obstructions of the efferent urinary tract, cystitis, infections and electrolyte imbalances.

Dermatological: It is ordinarily advisable to inform patients in advance of possible alopecia, a frequent complication of cyclophosphamide therapy. Regrowth of hair can be expected, although occasionally the new hair may be of a different colour or texture. The skin and fingernails may become darker during therapy. Nonspecific dermatitis has been reported to occur with cyclophosphamide.

Monitoring: Cyclophosphamide may be safely used in routine therapy if simple precautions are taken to avoid irreversible damage to the bone marrow. Weekly clinical and haematological examinations should be made. Total and differential blood cell counts and estimation of haemoglobin levels are essential. Many patients develop leucopenia and neutropenia during treatment. Counts should be done every two days if the leucocyte count is less than 3000/mm$^3$, and under some circumstances daily controls may be necessary. If signs of myelosuppression are evident, it is recommended that the red blood cell and platelet counts be checked. The lymphocyte and neutrophil counts usually return to normal levels upon completion of drug therapy.

Urinary sediment should also be checked regularly for the presence of erythrocytes.

Effects on ability to drive and operate machinery: Due to the possibility of side effects when cyclophosphamide is administered, e.g., nausea, vomiting which may result in circulatory insufficiencies, the physician should individually decide on the patient’s ability to participate in traffic or to operate machinery.

Patients undergoing treatment with cyclophosphamide may experience undesirable effects (including, e.g., dizziness, blurred vision, visual impairment) which could affect the ability to drive or use machines. The decision to drive or operate machinery should be made on an individual basis.
ADVERSE REACTIONS

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)

Alopecia
Alopecia has been reported and may occur more commonly with increasing doses. Alopecia may progress to baldness. The hair can be expected to grow back after treatment with the drug or even during continued drug treatment, though it may be different in texture or colour.

Alcohol consumption may increase cyclophosphamide-induced vomiting and nausea.

Stomatitis
Administration of cyclophosphamide may cause stomatitis (oral mucositis). Current guidelines on measures for prevention and amelioration of stomatitis should be considered.

Paravenous Administration
The cytostatic effect of cyclophosphamide occurs after its activation, which takes place mainly in the liver. Therefore, the risk of tissue injury from accidental paravenous administration is low. 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.

NEOPLASMS, BENIGN AND MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS): Acute leukaemia (Acute myeloid leukaemia, Acute promyelocytic leukaemia), 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, Tumour 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, Anaemia; Febrile neutropenia, Lymphopenia, Disseminated intravascular coagulation, Haemolytic uremic syndrome (with thrombotic microangiopathy), Haemoglobin 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

METABOLISM AND NUTRITION DISORDERS: Hyponatremia, Fluid retention, Anorexia, Blood glucose increased, Blood glucose decreased

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: Visual impairment, Vision blurred, 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 haemorrhage, Myocardial infarction, Cardiac failure congestive, 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 oedema, Pleural effusion, Bronchospasm, Dyspnea, Hypoxia, Cough, Nasal congestion, Nasal discomfort, Oropharyngeal pain, Rhinorrhea, Sneezing

GASTROINTESTINAL DISORDERS: Enterocolitis haemorrhagic, Gastrointestinal haemorrhage, Acute pancreatitis, Colitis, Enteritis, Cecitis, Mucosal ulceration, Stomatitis, Diarrhoea, Vomiting, Constipation, Nausea, Abdominal pain, Abdominal discomfort, Parotid gland inflammation

HEPATOBLIARY DISORDERS: Veno-occlusive liver disease, 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 erythrodysaesthesia syndrome, Radiation recall dermatitis, Toxic skin eruption, Urticaria, Dermatitis, Rash, Blister, Pruritus, Erythema, Skin discoloration, Nail discoloration, Nail disorder, Alopecia, 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, Haemorrhagic cystitis, Haemorrhagic ureteritis, Bladder necrosis, Cystitis ulcerative, Bladder fibrosis, Bladder contracture, Haematuria, Nephrogenic diabetes insipidus, Cystitis, Atypical urinary bladder epithelial cells, Blood creatinine increased, Blood urea nitrogen increased.

PREGNANCY, PUERPERIUM, AND PERINATAL CONDITIONS: Premature labour

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: Infertility, Ovarian failure, Ovarian disorder, Ovulation disorder, Amenorrhea, Oligomenorrhea, Testicular atrophy, Azoospermia, Oligospermia, Blood estrogen decreased, Blood gonadotrophin increased

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

GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS: Multiorgan failure, General physical deterioration, Influenza-like illness, Injection/infusion site reactions (thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema), Pyrexia, Edema, Chest pain, Mucosal inflammation, Asthenia, Pain, Chills, Fatigue, Malaise, Headache

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

*Haematopoietic:* Leucopenia is an expected effect and ordinarily is used as a guide to therapy. It may occur with or without fever and carries the risk of secondary (sometimes life-threatening) infections. Thrombocytopenia and/or anaemia may occur in a few patients. These effects are almost always reversible when therapy is interrupted. More severe myelosuppression is to be expected in patients who have been pretreated with chemo- and/or radiotherapy and in patients with renal impairment. Combination treatment with other myelosuppressive agents may require dose adjustments.

*Gastrointestinal:* Anorexia, nausea or vomiting are common and are related to dose as well as individual susceptibility. Diarrhoea, constipation and inflammatory conditions of the mucosa (mucositis), ranging from stomatitis to ulcerations, occur with a rarer frequency. There are isolated reports of haemorrhagic colitis and jaundice occurring during therapy.
Genitourinary: Haemorrhagic cystitis, microhaematuria and macrohaematuria are dose-dependent complications of therapy with ENDOXAN and require interruption of treatment (See Warnings). Cystitis is initially abacterial, secondary bacterial colonisation may follow. Oedema of the bladder wall, suburethral bleeding, interstitial inflammation with fibrosis and a potential for sclerosis of the bladder wall have also been observed.

Renal lesions (in particular with a history of impaired renal function) are a rare side effect after high doses.

Gonadal suppression, resulting in amenorrhoea and lower levels of female sex hormones or azoospermia or persistent oligospermia, has been reported in a number of patients treated with cyclophosphamide and appears to be related to dosage and duration of therapy. This side effect, possibly irreversible, should be anticipated in patients treated with cyclophosphamide. It is not known to what extent cyclophosphamide may affect prepubertal gonads. Fibrosis of the ovary following cyclophosphamide therapy has also been reported.

Hepatic: Rare cases of disturbances of hepatic function have been reported that are reflected by an increase in the corresponding laboratory test values (SGOT, SGPT, gamma-GT, alkaline phosphatase and bilirubin).

Veno-occlusive disease (VOD) is observed in approximately 15-50% of patients receiving high dose cyclophosphamide in combination with busulfan or whole-body irradiation during allogeneic bone marrow transplantation. By contrast, VOD is only rarely observed in patients with aplastic anaemia who are receiving high dose cyclophosphamide alone. The syndrome typically develops 1-3 weeks after the transplantation and is characterised by sudden weight gain, hepatomegaly, ascites and hyperbilirubinaemia. Hepatic encephalopathy may also develop.

Known risk factors predisposing a patient to the development of VOD are pre-existing disturbances of hepatic function, hepatotoxic drug therapy concurrently with high dose (chemo)therapy and especially when the alkylating agent busulfan is an element of the conditioning therapy.

Pulmonary: In isolated cases, pneumonitis, interstitial pneumonia extending to chronic interstitial pulmonary fibrosis may develop.

Cardiac toxicity: Although a few instances of cardiac dysfunction have been reported following the use of recommended doses of cyclophosphamide, no causal relationship has been established. Cardiotoxicity manifesting as arrhythmias, ECG changes and LVEF (eg myocardial infarction) has been observed in some patients receiving high doses of cyclophosphamide ranging from 120 to 270 mg/kg administered over a period of a few days, usually as a part of an intensive antineoplastic multidrug regimen or in conjunction with transplantation procedures. In a few instances with high doses of cyclophosphamide, severe and sometimes fatal congestive heart failure has occurred within a few days after the first cyclophosphamide dose. Histopathological examination has primarily shown haemorrhagic myocarditis. No residual cardiac abnormalities as evidenced by electrocardiogram or echocardiogram appear to be present.
in patients surviving episodes of apparent cardiac toxicity associated with high doses of cyclophosphamide.

There is evidence that the cardiotoxic effect of cyclophosphamide may be enhanced in patients who have received previous radiation treatment of the heart region and adjuvant treatment with anthracyclines. Regular electrolyte controls are necessary and special caution is advised in patients with pre-existing heart disease. Cyclophosphamide has been reported to potentiate doxorubicin induced cardiotoxicity.

Wound healing: Cyclophosphamide may interfere with normal wound healing.

Inappropriate water retention: In high doses cyclophosphamide has been reported to cause inappropriate water retention, resulting in hyponatraemia, seizures and death. The effect is directly upon the renal tubule.

Other: Alopecia, and pigment changes of the palms, fingernails and soles have been reported (see Precautions).

In addition, the following side effects have been observed:
- inflammation of the skin and mucosa
- hypersensitivity reactions accompanied by fever, extending to shock in isolated cases
- transient blurred vision and attacks of dizziness
- acute pancreatitis may occur in isolated cases
- in very rare cases (<0.01%) severe reactions eg Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported.

Note: there are certain complications, such as thromboembolism, DIC (disseminated intravascular coagulation), or haemolytic uraemic syndrome (HUS), that may also be induced by the underlying disease, but that might occur with an increased frequency under chemotherapy that includes ENDOXAN.

INTERACTIONS

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 receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention. 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.
Interactions Affecting the Pharmacokinetics of Cyclophosphamide and its Metabolites

Reduced activation of cyclophosphamide may alter the effectiveness of cyclophosphamide treatment. Substances that delay activation of cyclophosphamide include

- Aprepitant
- Bupropion
- Busulfan: 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.
- Ciprofloxacin: When given prior to the treatment with cyclophosphamide (used for conditioning prior to bone marrow transplantation), ciprofloxacin has been reported to result in a relapse of the underlying disease.
- Chloramphenicol
- Fluconazole
- Itraconazole
- Prasugrel
- Sulfonamides
- Thiotepa: A strong inhibition of cyclophosphamide bioactivation by thiotepa in high dose chemotherapy regimens has been reported when thiotepa was administered 1 hour prior to cyclophosphamide.

An increase of the concentration of cytotoxic metabolites may occur with

- Allopurinol
- Chloral hydrate
- Cimetidine
- Disulfiram
- Glyceraldehyde
- Inducers of human hepatic and extrahepatic microsomal enzymes (e.g., cytochrome P450 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 such as rifampin, phenobarbital, carbamazepine, phenytoin, St. John’s wort, and corticosteroids.
- Protease inhibitors: Concomitant use of protease inhibitors may increase the concentration of cytotoxic metabolites. Use of protease inhibitor-based regimens was found to be associated with a higher incidence of infections and neutropenia in patients receiving cyclophosphamide, doxorubicin, and etoposide (CDE) than use of an NNRTI-based regimen.

Ondansetron

There have been reports of a pharmacokinetic interaction between ondansetron and high-dose cyclophosphamide resulting in decreased cyclophosphamide AUC.

Pharmacodynamic Interactions and Interactions of Unknown Mechanism Affecting the Use of Cyclophosphamide

Combined or sequential use of cyclophosphamide and other agents with similar toxicities can cause combined (increased) toxic effects.
Increased haematotoxicity and/or immunosuppression may result from a combined effect of cyclophosphamide and, for example
- ACE inhibitors: ACE inhibitors can cause leukopenia.
- Natalizumab
- Paclitaxel: Increased haematotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion.
- Thiazide diuretics
- Zidovudine

Increased cardiotoxicity may result from a combined effect of cyclophosphamide and, for example
- Anthracyclines
- Cytarabine
- Pentostatin
- Radiation therapy of the cardiac region
- Trastuzumab

Increased pulmonary toxicity may result from a combined effect of cyclophosphamide and, for example
- Amiodarone
- G-CSF, GM-CSF (granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor): Reports suggest an increased risk of pulmonary toxicity in patients treated with cytotoxic chemotherapy that includes cyclophosphamide and G-CSF or GMCSF.

Increased nephrotoxicity may result from a combined effect of cyclophosphamide and, for example
- Amphotericin B
- Indomethacin: Acute water intoxication has been reported with concomitant use of indomethacin.

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

Other interactions

Etanercept
In patients with Wegener’s granulomatosis, the addition of etanercept to standard treatment, including cyclophosphamide, was associated with a higher incidence of non cutaneous solid malignancies.

Metronidazole
Acute encephalopathy has been reported in a patient receiving cyclophosphamide and metronidazole. Causal association is unclear. In an animal study, the combination of cyclophosphamide with metronidazole was associated with increased cyclophosphamide toxicity.
Tamoxifen
Concomitant use of tamoxifen and chemotherapy may increase the risk of thromboembolic complications.

Interactions Affecting the Pharmacokinetics and/or Actions of Other Drugs

Bupropion
Cyclophosphamide metabolism by CYP2B6 may inhibit bupropion metabolism.

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

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

Depolarizing muscle relaxants
Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity. Prolonged apnoea may occur with concurrent depolarizing muscle relaxants (e.g., succinylcholine). If a patient has been treated with cyclophosphamide within 10 days of general anaesthesia, the anaesthesiologist should be alerted.

Digoxin, β-acetyldigoxin
Cytotoxic treatment has been reported to impair intestinal absorption of digoxin and β-acetyldigoxin tablets.

Verapamil
Cytotoxic treatment has been reported to impair intestinal absorption of orally administered verapamil.

The rate of metabolism and the leucopenic activity of cyclophosphamide are reportedly increased by chronic administration of high doses of phenobarbitone.

Prior or concurrent treatment with phenytoin, benzodiazepines or chloral hydrate involves the possibility of microsomal liver enzyme induction.

When oral hypoglycaemics are given concomitantly with cyclophosphamide the reduction in the blood sugar level may be potentiated.

If cyclophosphamide and allopurinol or hydrochlorothiazide are given concomitantly there may be an increase in bone-marrow depression.

The fall in the pseudocholinesterase level during treatment with cyclophosphamide leads to a potentiation of the action of suxamethonium. Fairly prolonged apnoea is therefore possible.
Since cyclophosphamide shows immunosuppressive effects, the patient can be expected to exhibit a diminished response to any vaccination; injection with activated vaccines may be accompanied by vaccine-induced infection.

Concomitant administration of chloramphenicol leads to a prolonged half-life of cyclophosphamide and to a delayed metabolism.

Anthraclycline treatment may intensify the potential cardiotoxicity of cyclophosphamide. An intensification of the cardiotoxic effect may also occur after previous radiotherapy of the cardiac region.

Concomitant administration of indomethacin should be performed very carefully, since an acute water intoxication has been reported.

In general, patients receiving treatment with cyclophosphamide should abstain from drinking alcoholic beverages.

Because grapefruit contains a compound that may impair the activation of cyclophosphamide and thereby its efficacy, the patient must not eat any grapefruit or drink grapefruit juice.

The physician should be alert for possible drug interactions, desirable or undesirable, involving cyclophosphamide, even though cyclophosphamide has been successfully used concurrently with other drugs, including other cytotoxic drugs.

**OVERDOSE**

Large acute overdosage causes nausea, vomiting and prostration, depression of white blood cells and other formed elements in the blood, alopecia, and occasionally cystitis which can be prevented in many cases by giving the uroprotector UROMITEXAN (mesna).

The patient becomes immunologically unprotected, and secondary sepsis may supervene. Thrombocytopenia may predispose to bleeding episodes.

There is no specific antidote for an overdosage of cyclophosphamide. Measures should be taken to evacuate the unabsorbed material from the gastrointestinal tract or dialysis can be performed. Prevention of the infection during any period of depressed bone marrow function should receive attention. Treatment of nausea and vomiting is symptomatic. The alopecia may ordinarily be expected to be reversed after a period of time.

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 haematotoxicity in particular.
Cyclophosphamide and its metabolites are dialyzable. Therefore, rapid haemodialysis 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.

**DOSAGE AND ADMINISTRATION**

*Antineoplastic therapy:* Chemotherapy with cyclophosphamide, as with other drugs used in cancer chemotherapy, is potentially hazardous and fatal complications can occur. It is recommended that it be administered only by physicians aware of the associated risks. Therapy may be aimed at either induction or maintenance of remission.

Dosage must be individualised.

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 haematopoiesis 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.

Activation of cyclophosphamide requires hepatic metabolism; therefore, oral and intravenous administrations are preferred.

*Parenteral Use:* Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

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.
If injected directly, cyclophosphamide for parenteral administration should be reconstituted with physiological saline (0.9% sodium chloride). Cyclophosphamide, reconstituted in water, is hypotonic and should not be injected directly. Before parenteral administration, the substance must be completely dissolved.

**Induction therapy:** The usual initial intravenous loading dose for patients with no haematological deficiency is 40 to 50mg/kg. This total initial intravenous loading dose usually is given in divided doses over a period of two to five days. Patients with any previous treatment that may have compromised the functional capacity of the bone marrow, such as X-ray or cytotoxic drugs, and patients with tumour infiltration of the bone marrow may require reduction of the initial loading dose by one third to one-half.

A marked leucopenia is usually associated with the above doses but recovery usually begins after 7 to 10 days. The white blood cell count should be monitored closely during induction therapy. If initial therapy is given orally, a dose of 1 to 5 mg/kg/day can be administered depending on tolerance by the patient.

**Maintenance therapy:** It is frequently necessary to maintain chemotherapy in order to suppress or retard neoplastic growth. A variety of schedules has been used:

- 1 to 5mg/kg orally daily;
- 10 to 15mg/kg intravenously twice weekly
- 3 to 5mg/kg intravenously twice weekly

Unless the disease is unusually sensitive to cyclophosphamide, it is advisable to give the largest maintenance dose that can be reasonably tolerated by the patient. The total leucocyte count is a good objective guide to regulating the maintenance dose. Ordinarily, a leucopenia of 3,000 to 4,000 cells/mm$^3$ can be maintained without undue risks of serious infection or other complications.

**Immunosuppressive therapy:** Daily doses used have been in the order of 1 to 3mg/kg orally depending upon response and toxicity.

**Impaired hepatic function:** 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.

**Impaired renal function:** Since cyclophosphamide is excreted in the urine, dosage adjustment may be necessary in patients with impaired renal function (see Pharmacokinetics, Excretion).

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.
**STABILITY AND SHELF-LIFE**

ENDOXAN powder for injection 500mg, 1g and 2g: Unopened vials have a shelf-life of 3 years when stored below 25°C and protected from light.

**Stability and compatibility of reconstituted and further diluted solutions**

Cyclophosphamide solution for injection should be prepared by reconstituting ENDOXAN powder for injection with 0.9% sodium chloride injection: 5mL to each 100mg of cyclophosphamide, resulting in a solution containing 20mg/mL of cyclophosphamide ie: 2% w/v. Shake the solution to dissolve the solids and allow to stand until clear. Cyclophosphamide solution for injection may be injected intravenously, or it may be infused intravenously when admixed with the following solutions: Glucose Injection 5% w/v, Sodium Chloride (0.9% w/v) with Glucose (5% w/v) Injection, or Fructose (5% w/v) Injection.

**Incompatibilities**

Benzyl alcohol-containing solutions can reduce the stability of cyclophosphamide.

**Warning**

Cyclophosphamide solution for injection does not contain an antimicrobial agent and care must be taken to ensure the sterility of this and further diluted solutions. In addition any solutions which are hazy, discoloured or which contain visible particulate matter should be discarded. The product is for single use in one patient only. Discard any residue.

Due to the drug’s toxic and mutagenic properties, cyclophosphamide injections must not be prepared by pregnant personnel.

Personnel preparing injections should wear surgical gloves and closed front surgical-type gown with knit cuffs. If spills occur, mop up with absorbent material and discard all contaminated waste matter in a thick polyethylene bag labelled ‘Cytotoxic waste for incineration at 1,100°C’.

**Instructions for Use and Handling, and Disposal**

The handling and preparation of cyclophosphamide should always be in accordance with current guidelines on safe handling of cytotoxic agents.

During transport or storage of ENDOXAN Powder for Injections, temperature influences can lead to melting of the active ingredient, cyclophosphamide. Vials containing melted substances are easily noticeable as the powder becomes a clear or yellow viscous liquid (usually found as connected phase or in droplets in the affected vials). Do not use injection vials with melted content.
Stability
Reconstituted cyclophosphamide solution for injection and further diluted solutions prepared by admixing this with the recommended fluids listed above, have been shown to be physically and chemically stable for up to 24 hours when stored below 25°C and protected from light. However to avoid microbiological contamination it is recommended that solutions are used as soon as possible after preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours.

PRESENTATION
Powder for Injection, 500mg, 1g and 2g: Single vials.

Poisons Schedule: S4

DATE
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