APPROVED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:
CYTOSAR™ 100 mg (Powder for Injection)
CYTOSAR™ 500 mg (Powder for Injection)
Water For Injection with benzyl alcohol 0,9 % m/v

COMPOSITION:
CYTOSAR™ 100 mg contains 100 mg Cytarabine per vial.
CYTOSAR™ 500 mg contains 500 mg Cytarabine per vial.
Cytosar 100 mg and 500 mg must be reconstituted with Water for Injection containing 0,9 % m/v benzyl alcohol. (Do not use this diluent for intrathecal use or for high dose therapy - SEE WARNINGS).

PHARMACOLOGICAL CLASSIFICATION:
A 26 Cytostatic agents

PHARMACOLOGICAL ACTION:
Tissue culture studies
CYTOSAR (cytarabine) is cytotoxic to a variety of mammalian cell lines in culture. Although inhibitory to growing mammalian cells, CYTOSAR is inactive at high concentrations against resting KB cells. Deoxycytidine delays or prevents the cytotoxic action of CYSTOSAR into DNA and RNA. Studies on the mechanism of cytotoxicity in-vitro suggest that the primary action of CYTOSAR is inhibition of deoxycytidine synthesis, although inhibition of cytidylic acid kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytocidal actions. CYTOSAR has been reported to cause chromosome breaks in human leukocytes *in-vitro*. It inhibits DNA synthesis in mammalian cell cultures. CYTOSAR is immunosuppressive as demonstrated by inhibition of hemaglutinin synthesis in mice.

Drug fate and metabolism
There is in human liver and kidney an enzyme which deaminates CYTOSAR (cytarabine) to arabinofuranosyl uracil, an inactive metabolite. After intravenous administration of CYTOSAR to humans, only 5-8 % of the administered dose is excreted unaltered in the urine within 12 -24 hours; approximately 90 % of the dose is excreted as the deamination product, arabinofuranosyl uracil. CYTOSAR appears to be metabolized rapidly, primarily by the liver and perhaps by the kidney and to be excreted mainly as the deamination product. After single high intravenous doses, blood levels fall to unmeasurable levels within 15 minutes, in most patients. Some patients have no demonstrable circulating medication as early as 5 minutes after injection.

INDICATIONS:
CYTOSAR (cytarabine) is indicated for induction and maintenance of remission in acute non-lymphocytic leukaemia of both adults and children. It is also indicated in the treatment of acute lymphocytic leukaemia and chronic myelocytic leukaemia (blast phase).

CYTOSAR may be used alone or in combination with other antineoplastic agents. It is more effective when used in combination therapy with other agents.
Children with non-Hodgkin's lymphoma have benefited from a combination medication program that included CYTOSAR.

CYTOSAR alone or in combination with other medicines is used intrathecally for prophylaxis or treatment of meningeal leukaemia.
CYTOSAR in high doses (2 – 3 g/m^2) may be effective in some cases of refractory leukaemia and relapsed acute leukaemia, although systemic toxicity, especially of the central nervous system, may be high.

CONTRA-INDICATIONS:
CYTOSAR (cytarabine) is contra-indicated in patients with depressed bone marrow.
Hypersensitivity to cytarabine.

Lactation
Safety in lactation has not been established. Patients on CYTOSAR should not breastfeed.

Use in pregnancy
CYTOSAR is known to be teratogenic.
Infants can be premature or of low birth weight. Cases of congenital abnormalities have been reported with upper and lower distal limb defects and with extremity and ear deformities.
Infants can have various problems in the neonatal period, including pancytopenia, depression of white blood cells, hematocrit or platelets, electrolyte abnormalities, eosinophilia and increased lgM levels and hyperpyrexia possibly due to sepsis. Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, a patient who is or who may become pregnant while on CYTOSAR, should be apprised of the potential risk to the foetus and the advisability of pregnancy continuation. There is a definite risk if therapy is initiated during the second or third trimester.

WARNINGS:
Only physicians experienced in cancer chemotherapy should use CYTOSAR. For induction therapy, patients should be treated in a facility with laboratory and supportive resources sufficient to monitor medicine tolerance and protect and maintain a patient compromised by toxicity of the agent. The main toxic effect of CYTOSAR is bone marrow suppression with leukopenia, thrombocytopenia and anaemia.

Other manifestations include nausea, vomiting, diarrhoea and abdominal pain, oral ulceration and hepatic dysfunction. Seizures and other manifestations of neurotoxicity may occur after intrathecal administration.

The physician must judge possible benefit to the patient against known toxic effects of this medicine in considering the advisability of therapy with CYTOSAR. Before making this judgement or beginning treatment, the physician should be familiar with the following text:
CYTOSAR (cytarabine) is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing medicine-induced bone marrow suppression.
Patients receiving this medicine must be under close medical supervision and during induction therapy, should have leukocyte and platelet counts performed daily. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood.
Facilities should be available for management of complications, possibly fatal, of bone marrow suppression, (infection resulting from granulocytopenia and other impaired body defences and hemorrhage secondary to thrombocytopenia.) Anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation have been reported. This occurred immediately after the intravenous administration of CYTOSAR.

Severe, and at times fatal, cardiomyopathy,CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of CYTOSAR) has been reported following high dose (2 – 3 g/m^2) schedules of CYTOSAR **(See "SIDE-EFFECTS AND SPECIAL PRECAUTIONS")**

If high dose therapy is used or if given intrathecally do not use a diluent containing benzyl alcohol. Most clinicians reconstitute with preservative-free 0,9 % sodium chloride for injection and use immediately.
Benzyl alcohol is contained in the diluent for CYTOSAR 100 mg and 500 mg.
Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

DOSAGE AND DIRECTIONS FOR USE:
CYTOSAR (cytarabine) is not active orally. The schedule and method of administration varies with the program of therapy to be used. CYTOSAR may be given by intravenous infusion, injection, intrathecally or subcutaneously. Patients can sometimes tolerate higher total doses when they receive the medicine by rapid intravenous injection as compared to slow infusion, but no clear cut clinical advantage has been demonstrated by either. Toxicity necessitating dose alteration almost always occurs.
In many chemotherapeutic programs, CYTOSAR is used in combination with other cytotoxic medicines. The addition of these cytotoxic medicines has necessitated changes and dose alterations. The dosage schedules for combination therapy have been reported in the literature.

Dosage Schedules:
Acute non-lymphocytic leukaemia - induction of remission, adults and children:
CYTOSAR (cytarabine) – 100 mg/m^2 day by continuous infusion (Days 1 – 7) or 100 mg/m^2 infusion every 12 hours (Days 1 – 7) or until bone hyperplasia occurs.

Acute non-lymphocytic leukaemia - maintenance:
Adults: Maintenance programs are modifications of induction programs and in general, use similar schedules of medicine therapy as were used during induction. Most programs have a greater time spacing between courses of therapy during remission maintenance.
Children: Where the adult dosage is stated in terms of body mass or surface area, the children's dosage may be calculated on the same basis. When specified amounts of a medicine are indicated for the adult dosage, these should be adjusted for children on the basis of factors such as age, body mass or body surface area.

Acute Lymphocytic Leukaemia:
In general, dosage schedules are similar to those used in acute non-lymphocytic leukaemia with some modifications.

Meningeal leukaemia - intrathecal use
The most frequently used dose was 30 mg/m^2 every 4 days until cerebrospinal fluid findings were normal, followed by one additional treatment.

Combined chemotherapy or high dose therapy
Before instituting a program of combined chemotherapy or high dose therapy, the physician should be familiar with the literature, adverse reactions, precautions, contra-indications and warnings applicable to all the medicines involved in the program.

High-dose therapy: 2 – 3 g/m^2 as an infusion over 1 – 3 hours given every 12 hours for 2 – 6 days with or without additional cancer chemotherapeutic agents, has been shown to be effective in the treatment of poor-risk leukaemia, refractory leukaemia and relapsed acute leukaemia

Non-Hodgkin's lymphoma in children:
CYTOSAR has been used as part of a multi-medicine program to treat non-Hodgkin's lymphoma in children.

Dosage modification:
The dosage of CYTOSAR must be modified or suspended when signs of serious hematologic depression appear. In general consider discontinuing the medicine if the patient has less than
50 000 platelets or 1 000 polymorphonuclear granulocytes/mm^3 in the peripheral blood. These guidelines may be modified depending on signs of toxicity in other systems and on the rapidity of fall in formed blood elements. Re-start the medicine when there are signs of marrow recovery and the above platelet and granulocyte levels have been attained. Withholding therapy until the patient's blood values are normal may result in escape of the patient's disease from control by the medicine.

Stability in infusion solutions:
CYTOSAR is stable for seven days at room temperature when admixed at 0.5mg/ml in glass IV bottles and plastic intravenous bags with, water for injection, 5 % dextrose injection, and 0.9% sodium chloride injection solutions. Also when similarly admixed at 8 - 32 mg/ml in glass intravenous bottles and plastic intravenous bags, cytarabine is stable for seven days at room temperature, -20°C and 4°C in 5 % dextrose injection, 5 % dextrose in 0,2 % sodium chloride injection, and in 0,9 % sodium chloride injection solutions.

CYTOSAR 2 mg/ml is chemically stable in the presence of KCl equivalent to 50 mmol/500ml in dextrose 5 % in water and 0,9 % sodium chloride for up to 8 days.
CYTOSAR is also stable at room temperature and at refrigerated temperature (8°C) at a concentration of 0,2-1,0 mg/ml in the presence of sodium bicarbonate equivalent to 50 mmol/L in dextrose 5 % in water or dextrose 5 % in 0,2 % sodium chloride for seven days in Travenol glass bottles or viaflex bags.

Drug compatibilities:
CYTOSAR is compatible with the following medicines, at the specified concentrations: in dextrose 5 % in water for eight hours; CYTOSAR 0,8 mg/ml and cephalothin 1,0 mg/ml; CYTOSAR 0,4 mg/ml and prednisolone sodium phosphate 0,2 mg/ml; CYTOSAR 16 µg/ml and vincristine sulphate 4µg/ml is compatible in dextrose 5 % in water for 8 hours.

Drug incompatibilities:
CYTOSAR has been known to be physically incompatible with heparin, insulin, methotrexate, 5-fluorouracil, nafcillin, oxacillin, penicillin G, SOLU B and SOLU-MEDROL.

DIRECTIONS FOR USE OF THE AMPOULE:
No ampoule file is needed to open the ampoule. The neck of the ampoule is pre-scored at the point of constriction. A coloured dot on the ampoule helps to orientate the ampoule. Take the ampoule and face the coloured dot. The ampoule opens easily by placing the thumb on the coloured dot and gently pressing downwards as shown.

PICTURES

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
Because CYTOSAR (cytarabine) is a bone marrow suppressant, anaemia, leukopenia, thrombocytopenia, megaloblastosis and reduced reticulocytes can be expected as a result of its administration. The severity of these reactions are to a certain degree dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

Following 5-day constant infusions or acute injections of 50 mg/m^2 to 600 mg/m^2, white cell depression follows a biphasic course.

Regardless of initial count, dosage level, or schedule, there is an initial fall starting the first 24 hours with a nadir at days 7 - 9. This is followed by a brief rise which peaks around the twelfth day. A second and deeper fall reaches nadir at 15 - 24. Then there is a rapid rise to above baseline in the next 10 days.
Platelet depression is noticeable at 5 days with a peak depression occurring between days 12 - 15. Thereupon, a rapid rise to above baseline occurs in the next 10 days.

The CYTOSAR (Ara-C) Syndrome:
This is characterized by fever, myalgia, bone pain, chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 - 12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are deemed treatable, corticosteroids should be contemplated as well as continuation of therapy with **CYTOSAR**.

Frequent Adverse Reactions:

anorexia	hepatic dysfunction
nausea	fever
vomiting	rash
diarrhoea	thrombophlebitis
oral and anal inflammation or ulceration	bleeding (all sites)

Nausea and vomiting are most frequent following rapid intravenous injection and may continue for several hours after injection.

Other adverse reactions:

sepsis	abdominal pain
pneumonia	freckling
cellulitis at injection site	jaundice
skin ulceration	conjunctivitis (may occur with rash)
urinary retention	dizziness
renal dysfunction	alopecia
neuritis	anaphylaxis (see Warnings)
neural toxicity	allergic oedema
sore throat	pruritis
oesophageal ulceration	shortness of breath
oesophagitis	urticaria
chest pain	headache
pericarditis	

Severe and fatal central nervous system, gastro-intestinal and pulmonary toxicity, different from that seen with conventional therapy regimens of CYTOSAR, has been reported following high dose
(2 – 3 g/m^2) schedules of CYTOSAR. These reactions include corneal toxicity, and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eyedrop; cerebral and cerebellar dysfunction, including personality changes, somnolence and coma,
severe gastro-intestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis,
sepsis and liver abscess, pulmonary oedema, liver damage with increased hyperbilirubinemia; bowel necrosis; and necrotising colitis.
Peripheral motor and sensory neuropathies have been reported after consolidation with high dose CYTOSAR in combination therapy.

An increase in cardiomyopathy with subsequent death has been reported following experimental high dose CYTOSAR and cyclophosphamide therapy when used for bone marrow transplant preparation.

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary oedema and radiographically pronounced cardiomegaly has been reported following high dose therapy with CYTOSAR in relapsed leukaemia. A fatal outcome has also been reported.
Acute pancreatitis has been reported to occur in patients being treated with CYTOSAR in combination with other medicines.
Severe skin rash, leading to desquamation, has been reported. Complete alopecia is more commonly seen with high dose therapy than with standard treatment.

Infectious complications:
Viral, bacterial, fungal, parasitic, or saprophytic infections in any location of the body, may be associated with the use of CYTOSAR alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.
CYTOSAR given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. Modification of the anti-leukaemia therapy may be necessary.
Reactions after intrathecal administration are nausea, vomiting and fever. Paraplegia has been reported as well as necrotizing leuko-encephalopathy. Neurotoxicity has been reported and blindness occurred in patients in remission whose treatment had consisted of combination systemic chemotherapy, prophylactic central nervous system radiation and intrathecal CYTOSAR.
Focal leukaemic involvement of the central nervous system may not respond to intrathecal CYTOSAR and may better be treated with radiotherapy.
Diffuse interstitial pneumonitis without clear cause has been reported.

Carcinogenesis, mutagenesis, impairment of fertility
Extensive chromosomal damage, including chromatoid breaks has been produced by cytarabine, and malignant transformation of rodent cells in culture has been reported.

Precautions:
Patients receiving CYTOSAR (cytarabine) must be monitored closely. Daily platelet and leukocyte counts and frequent bone marrow examination are mandatory. Consider suspending or modifying therapy when medicine-induced marrow depression has resulted in a platelet count under 50 000 or a polymorphonuclear granulocyte count under 1 000/m^3.
Counts of formed elements in the peripheral blood may continue to fall after the medicine is stopped and reach lowest values after medicine free intervals of 12 to 24 days. When indicated, re-start therapy when definite signs of marrow recovery appear (on successive bone marrow studies). Patients whose medicine is withheld until "normal" peripheral blood values are attained may escape from control.

When large intravenous doses are given quickly, patients are frequently nauseated and may vomit for several hours post-injection. This problem tends to be less severe when the drug is infused.

The human liver apparently detoxifies a substantial fraction of an administered dose. In particular, patients with renal or hepatic function impairment may have a higher likelihood of CNS toxicity after high-dose treatment with CYTOSAR. Use the medicine with caution and at reduced dose in patients whose liver function is poor. Regular checks of bone marrow, liver and kidney functions should also be performed in patients receiving CYTOSAR.

Patients treated with high-dose CYTOSAR should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurological disorders.

CYTOSAR may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

Drug interactions:
A reversible decrease in steady state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyl digoxin and chemotherapy regimens containing cyclophosphamide, vincristine and predisone with or without CYTOSAR or procarbazine. Steady-state digitoxin plasma concentration did not appear to change. Therefore, monitoring of plasma digoxin levels may be indicated in patients receiving similar combination chemotherapy regimens.
The utilisation of digitoxin for such patients may be considered as an alternative.

An *in-vitro* interaction study between gentamycin and cytarabine showed cytarabine related antagonism for the susceptibility of *K.pneumoniae* strains. It was suggested that it may be advisable to re-evaluate the antibacterial therapy.
Possible inhibition of efficacy of fluorocytosine, ascribed to potential competitive inhibition of its uptake, has been suggested.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
There is no antidote for CYTOSAR overdosage.
The major toxicity with this dose, other than reversible bone marrow suppression, has been corneal, cerebral and cerebellar dysfunction. Doses of 4,5 g/m^2 intravenous infusion over 1 hour every 12 hours for 12 doses have caused irreversible central nervous system toxicity and death.
Treatment is symptomatic and supportive.

IDENTIFICATION:
CYTOSAR (cytarabine) is available as a freeze-dried preparation.
CYTOSAR 100 mg and 500 mg are in multidose vials.
Water For Injection (with benzyl alcohol 0,9 % m/v) is available in vials of 5 ml and 10 ml.

PRESENTATION:
100 mg vial plus 5 ml water for injection (with benzyl alcohol 0,9 % m/v)
500 mg vial plus 10 ml water for injection (with benzyl alcohol 0,9 % m/v)

STORAGE INSTRUCTIONS:
Store at room temperature (15°C - 30°C).
Once reconstituted, the 100 mg and 500 mg strengths should be stored at room temperature (15°C - 30°C) and used within 48 hours.
Discard any solution in which a slight haze develops.
Keep out of reach of children.

REGISTRATION NUMBERS:
CYTOSAR™ 100 mg: H2757 (Act 101/1965)
CYTOSAR™ 500 mg: T/26/47
Bacteriostatic Water For Injection with benzyl alcohol 0,9 % m/v: H/34/60

NAME AND BUSINESS OF THE APPLICANT:
Pfizer Laboratories (Pty) Ltd
85 Bute Lane
Sandton 2196
South Africa

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