Cytosar ®

CYTARABINE

100 mg/5 ml Powder and Solvent for Injectable Solution
500 mg/10 ml Powder and Solvent for Injectable Solution

Reference market: Italy

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CYTOSAR 100 mg/5 ml Powder and Solvent for Injectable Solution
CYTOSAR 500 mg/10 ml Powder and Solvent for Injectable Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CYTOSAR	100 mg	500 mg
Each glass vial of lyophilized product contains:		
cytarabine	100 mg	500 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for injectable solution for intravenous and subcutaneous use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CYTOSAR is indicated for inducing remission in acute myeloid leukaemia of adults and children.
It is indicated secondarily in the treatment of other proliferative forms of the leucocyte series.

4.2 Posology and method of administration

Posology

Induction therapy in acute non-lymphocytic leukaemia
The usual dose of cytarabine in association with other anti-blastic drugs is 100 mg/m^2/day in continuous intravenous infusion (days 1-7) or 100 mg/m^2 I.V. every 24 hours (days 1-7).

For use in acute lymphocytic leukaemia one should consult the relative literature for the current recommendations.

Method of administration
CYTOSAR is not active if taken orally. The dosage regimen and method of administration vary depending on the therapeutic programme adopted.
CYTOSAR can be administered by rapid intravenous injection or slow intravenous infusion and by subcutaneous injection.

In some patients thrombophlebitis has occurred at the site of the intravenous infusion and in rare cases pain and inflammation have been experienced at the subcutaneous injection site. Patients can tolerate greater total doses when the drug is administered by means of rapid intravenous injection as opposed to slow infusion. In fact, in this case, rapid inactivation of the drug occurs with reduction of the exposure time of both the normal and the neoplastic cells.
The normal and the neoplastic cells appear to respond in a more or less parallel manner to these different methods of administration and no clear difference has emerged from a clinical point of view.

Drug Compatibilities

Cytarabine is compatible with the following drugs, at the specified concentrations, in Dextrose 5% in water for eight hours: cytarabine 0.8 mg/ml and Sodium Cephalothin 1.0 mg/ml; cytarabine 0.4 mg/ml and prednisolone sodium phosphate 0.2 mg/ml; cytarabine 16 mcg/ml and vincristine sulfate 4 mcg/ml, cytarabine 0.4 mg/ml and methotrexate 0.2mg7ml.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Therapy with CYTOSAR should not be carried out in patients with pre-existing bone marrow depression induced by other drugs, unless such therapy is considered the best therapeutic choice for the patient.
Degenerative and toxic encephalopathies, particularly following the use of methotrexate or ionizing radiation treatment, as well as in the presence of very low blood count due to causes other than cancer.

4.4 Special warnings and precautions for use

Pediatric patients

The safety of this medicinal product in children has not been established.

Warnings

CYTOSAR should be used only by clinicians specialised in anti-neoplastic chemotherapy. For the induction therapy the patients should be hospitalised in departments that have the necessary equipment and laboratories to guarantee adequate control of the tolerability of the drug and protect or keep alive a patient who is functionally impaired from the toxicity of the drug.

Not to be used in ascertained or presumed pregnancy.

The main secondary effect of CYTOSAR is myelo-inhibition with, as a consequence, leucopenia, thrombocytopenia and anaemia.

Secondary manifestations of lesser importance are represented by nausea, vomiting, diarrhoea, abdominal pain and ulceration of the oral cavity; alterations in liver function are also possible.

The physician should carefully weigh up the possible benefits that the patient may gain from the treatment against the secondary reactions that the drug may induce.

The physician should have thorough knowledge of the contents of the information sheet before expressing his/her opinion as to whether or not this treatment should be prescribed.

Cytarabine displayed carcinogenic effects in animals. The possibility of a similar effect should be taken into account when setting-up long-term treatment of the patient.

Hematologic Effects

CYTOSAR has a strong myelo-inhibitive action; the severity depends on the dose of the drug and schedule of administration. Therapy should be commenced with caution in patients with pre-existing drug-induced bone marrow depression. Patients treated with CYTOSAR should be kept under close medical observation and during therapy there should be a daily count of the white blood cells and the platelets. Bone marrow tests should be carried out frequently after the disappearance of the blastic forms 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 haemorrhage secondary to thrombocytopenia).
Therapy with CYTOSAR should be modified or suspended when the platelets drop to below 50,000/mm3 or when the granulocytes drop to below 1,000/mm^3.

The count of the elements formed in the peripheral blood can continue to diminish after discontinuation of the drug and can reach the nadir after an interval of 12-24 days from when administration is terminated.

Treatment can be re-introduced when there are precise signs of recovery of bone marrow activity with an increase in the platelets or the granulocytes.
Waiting until the haematology values have returned to normal before re-starting the treatment can mean losing control of the disease.

Different precautions may be taken in the case of severe signs of toxicity in any other apparatus/system or for a rapid drop in the elements formed in the peripheral blood.

Anaphylactic reactions have occurred with cytarabine treatment. Anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine.

High Dose Schedules not authorized (2-3 g/m^2)
CYTOSAR administered according to high dosage regimens (2-3 g/m^2) has caused severe toxicity, at times fatal, of the Central Nervous System, the gastrointestinal apparatus and the lungs (different from that seen with conventional therapy regimens of cytarabine).

These reactions include reversible corneal toxicity and haemorrhagic conjunctivitis which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop; cerebral and cerebellar dysfunctions, usually reversible, with personality changes, drowsiness, convulsion and coma; severe gastrointestinal ulceration, including intestinal cystoid pneumatosis leading to peritonitis; sepsis and hepatic abscesses; liver damage with raised hyperbilirubinaemia; necrosis of the intestine and necrotizing colitis; pulmonary oedema.

Severe and sometimes fatal pulmonary toxicity, adult respiratory distress syndrome and pulmonary edema have occurred following high dose schedules with cytarabine therapy.
Following experimental therapy with high doses of cytarabine for the treatment of relapses of leukaemia, a syndrome of sudden respiratory failure was reported, which rapidly progressed to pulmonary oedema and cardiomegaly resulting evident from radiography. This syndrome can have a fatal outcome.

Cases of cardiomyopathy with fatal consequences have occurred following therapy with high experimental doses of cytarabine in association with cyclophosphamide for the preparation for bone marrow transplantation: this reaction can depend on the therapeutic regimen.

Peripheral motor and sensory neuropathies after consolidation with high doses of cytarabine, daunorubicin, and asparaginase have occurred in adult patients with acute non lymphocytic leukemia. Patients treated with CYTOSAR at high doses should be kept under observation for the possible onset of neuropathies, in consideration of the fact that changes in the dosage regimen may be necessary in order to avoid irreversible neurological changes.

Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more

commonly seen with high dose therapy than with standard treatment programs of cytarabine. The administration of high doses by rapid intravenous infusion is frequently accompanied by nausea and sometimes by vomiting that can continue even for several hours. This problem is generally less when the drug is administered by slow infusion.

Conventional Dose Schedules
Abdominal tenderness (peritonitis) and guaiac positive colitis, with concurrent neutropenia and thrombocytopenia, have been reported in patients treated with conventional doses of cytarabine in combination with other drugs. Patients have responded to nonoperative medical management. Delayed progressive ascending paralysis resulting in death has been reported in children with AML following intrathecal and intravenous cytarabine at conventional doses in combination with other drugs.

Hepatic and/or renal Impairment
The human liver apparently detoxifies a substantial fraction of an administered dose of cytarabine. In particular, patients with renal or hepatic function impairment may have a higher likelihood of CNS toxicity after high-dose treatment with cytarabine. Use the drug with caution and possibly at reduced doses in patients whose liver or kidney function is poor.
Patients on treatment with CYTOSAR should be subjected to periodic controls of bone marrow activity and liver and kidney function.

Neurological Damage
Cases of severe neurological adverse reactions that ranged from headache to paralysis, coma and stroke-like episodes have been reported mostly in juveniles and adolescents given intravenous cytarabine in combination with intrathecal methotrexate.

Tumor Lysis Syndrome
As with all cytotoxic drugs, CYTOSAR may induce a state of hyperuricaemia secondary to the rapid lysis of the newly-formed cells. The uric acid levels should, therefore, be regularly monitored and suitable therapeutic measures adopted, should this prove necessary.

Pancreatitis
Acute pancreatitis has been reported to occur in patients being treated with cytarabine in combination with other drugs.

Immunosuppressant Effects/Increased Susceptibility to Infections Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cytarabine, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving cytarabine. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

4.5 Interactions with other medicinal products and other forms of interaction

Digoxin
Reversible reductions in the plasma concentrations at the steady-state of digoxin and of the excretion of renal glycoside have been observed in patients receiving beta-acetyldigoxin with chemotherapeutic regimens containing cyclophosphamide, vincristine and prednisone, with or without CYTOSAR or procarbazine. The plasma concentrations at the steady-state of digitoxin do not appear to be changed. Monitoring of the plasma levels of digoxin may therefore be indicated in patients on treatment with this form of chemotherapy.
The use of digitoxin in such patients can be considered as an alternative.

Gentamicin

Cytarabine has shown antagonism *in vitro* with gentamicin in the susceptibility of K. pneumoniae strains. Therefore, in patients in treatment with cytarabine who present a K. pneumoniae infection treated with gentamicin, the absence of a prompt therapeutic response may indicate the need for a re-assessment of the antibacterial therapy.

Fluorocytosine
It is possible for the efficacy of fluorocytosine to be inhibited during therapy with CYTOSAR, due to the potential competitive inhibition of its uptake.

Methotrexate
Intravenous cytarabine given concomitantly with intrathecal methotrexate may increase the risk of severe neurological adverse reactions such as headache, paralysis, coma and stroke like episodes (see section **Error! Reference source not found.**4.4).

4.6 Fertility, Pregnancy and lactation

Pregnancy
There are no studies on the use of cytarabine in pregnant women. Cytarabine is known to be teratogenic in some animal species. Use of this drug in women who are or who may become pregnant should be undertaken only after due consideration of potential benefit and potential hazard to both mother and child. Women of childbearing potential should be advised to avoid becoming pregnant.
Normal infants have been born to mothers exposed to cytarabine during pregnancy (alone or in combination with other drugs); some of these infants were premature or of low birthweight. Some of the normal infants were followed up at ages ranging from six weeks to seven years following exposure, and showed no abnormalities. One apparently normal infant died at 90 days of gastroenteritis.

Congenital abnormalities have been reported, particularly when the fetus has been exposed to systemic therapy with cytarabine during the first trimester. These include upper and lower distal limb defects, and extremity and ear deformities.

Reports of pancytopenia, leukopenia, anemia, thrombocytopenia, electrolyte abnormalities, transient oesinophilia, increased IgM levels and hyperpyrexia, sepsis and death have occurred during the neonatal period to infants exposed to cytarabine *in* utero. Some of these infants were also premature.

Therapeutic abortions have been done in pregnant women on cytarabine. Normal fetuses have been reported while other reported fetal effects included enlarged spleen and Trisomy C chromosome abnormality in the chorionic tissue.

Because of the potential risk of abnormalities caused by the cytotoxic therapy, especially during the first three months of pregnancy, pregnant women or those who fall pregnant while undergoing treatment with CYTOSAR must be informed of the potential risks for the foetus and advised on whether or not to continue with the pregnancy. These risks, while still present, are considerably reduced if the therapy is commenced during the second or third trimester of pregnancy. While normal babies have been born to patients treated during the entire period of pregnancy, it is advisable for these babies to be kept under medical observation.

Breastfeeding
There are no data available regarding either human beings or animals on the excretion of cytarabine in breast-milk. It is advisable, therefore, to interrupt breastfeeding or suspend the treatment with CYTOSAR, taking into consideration the importance of the drug for the mother.

Fertility
No fertility studies have been carried out to evaluate the reproductive toxicity of cytarabine. Gonadal inhibition, with consequent amenorrhea or azoospermia, may be manifested in patients taking cytarabine, particularly concomitant to alkylating agents. These effects generally seem to be correlated to dose and duration of treatment, and may be irreversible (see section 4.8). Given that cytarabine possesses a mutagenic effect capable of inducing a chromosomal damage in human spermatozoa, male patients undergoing treatment with cytarabine and their partners should be advised to use a reliable method of contraception both during and up until six months after completion of treatment.

4.7 Effects on ability to drive and use machines

Cytosar does not affect, or has a negligible effect, on the ability to drive or to use machines. Patients receiving chemotherapy may have an impaired ability to drive or to operate machinery, and should therefore be warned of this possibility and advised to avoid these tasks if such an effect is manifested.

4.8 Undesirable effects

Summary of the safety profile (see also section 4.4)

Blood and lymphatic system disorders
Since cytarabine is a cytotoxic agent that acts as an inhibitor of the bone marrow, the expected adverse reactions are those common to drugs of this class, such as: anaemia, leucopenia, thrombocytopenia, megaloblastosis, reticulocytopenia, qualitative changes in the cellular population of the bone marrow.

The severity of these reactions depends on the dosage regimen adopted and the size of the dose.

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 days 15-24. Then there is 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.

Infections and infestations
Viral, bacterial, mycotic, parasitic or saprophytic infections at any point in the body, can be associated with the use of cytarabine alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity.
These infections can be mild, but also severe and at times with a fatal outcome.

Musculoskeletal and connective tissue disorders

Cytarabine syndrome
A “cytarabine syndrome” has been described, characterized by fever, myalgia, pain in the bones, occasionally thoracic pain, maculopapular rash, conjunctivitis and malaise. It usually appears 6-12 hours after administration. The administration of corticosteroids has proved effective in the treatment/prevention of this syndrome.
If the symptoms of the syndrome are held to be treatable, one should consider combining the use

of corticosteroids with continuation of the therapy with cytarabine.

The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency. Frequencies are defined as: Very common (≥1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1000, <1/100), Rare (≥ 1/10.000, < 1/1.000), and Frequency not known (cannot be estimated from available data).

Adverse Reactions Table (Conventional and High Dose Therapy)

Infections and Infestations:	
Very common	Sepsis, pneumonia, infections[a]
Not known	Injection site cellulitis
Blood and Lymphatic System Disorders:	
Very common	Bone marrow failure, thrombocytopenia, anaemia, anaemia megaloblastic, leukopenia, reticulocyte count decreased
Immune System Disorders:	
Not known	Anaphylactic reaction, allergic oedema
Metabolism and Nutrition Disorders:	
Not known	Decreased appetite
Nervous System Disorders:	
Not known	Neurotoxicity, neuritis, dizziness, headache
Eye Disorders:	
Not known	Conjunctivitis[b], hemorrhagic conjunctivitis
Cardiac Disorders:	
Not known	Pericarditis, sinus bradycardia
Vascular Disorders:	
Not known	Thrombophlebitis
Respiratory, Thoracic and Mediastinal Disorders:	
Not known	Dyspnoea, oropharyngeal pain
Gastrointestinal Disorders:	
Very common	Stomatitis, mouth ulceration, anal ulcer, anal inflammation, diarrhoea, vomiting, nausea, abdominal pain
Not known	Pancreatitis, oesophageal ulcer, oesophagitis
Hepatobiliary Disorders:	
Very common	Hepatic function abnormal
Not known	Jaundice
Skin and Subcutaneous Tissue Disorders:	
Very common	Alopecia, skin rash
Common	Skin ulcer
Not known	Palmar-plantar erythrodysaesthesia syndrome, urticaria, pruritus, ephelides
Musculoskeletal, Connective Tissue and Bone Disorders:	
Very common	Cytarabine syndrome
Renal and Urinary Disorders:	
Not known	Renal impairment, urinary retention

General Disorders and Administration Site Conditions:	
Very common	Pyrexia
Not known	Chest pain, injection site reaction[c]
Investigations:	
Very common	Biopsy bone marrow abnormal, blood smear test abnormal
[a]may be mild, but can be severe and at times fatal [b]may occur with rash and may be hemorrhagic with high dose therapy [c]pain and inflammation at subcutaneous injection site	

High experimental doses not authorised (see also section 4.4)

CYTOSAR administered according to experimental high dosage regimens (2-3g/m^2) has caused severe toxicity, at times fatal, of the Central Nervous System, the gastrointestinal apparatus and the lungs (different from that encountered with standard therapeutic regimens).

Adverse Reactions Table (High Dose Therapy)

Infections and Infestations:	
Not known	Liver abscess
Psychiatric Disorders:	
Not known	Personality change[a]
Nervous System Disorders:	
Very common	Cerebral disorder, cerebellar disorder, somnolence
Not known	Coma, convulsion, peripheral motor neuropathy, peripheral sensory neuropathy
Eye Disorders:	
Very common	Corneal disorder
Cardiac Disorders:	
Not known	Cardiomyopathy[b]
Respiratory, Thoracic and Mediastinal Disorders:	
Very common	Acute respiratory distress syndrome, pulmonary oedema
Gastrointestinal Disorders:	
Common	Necrotising colitis
Not known	Gastrointestinal necrosis, gastrointestinal ulcer, pneumatosis intestinalis, peritonitis
Hepatobiliary Disorders:	
Not known	Liver injury, hyperbilirubinaemia
Skin and Subcutaneous Tissue Disorders:	
Common	Skin exfoliation,

[a]Personality change was reported in association with cerebral and cerebellar dysfunction.
[b]With subsequent death

Other Adverse Reactions

Ten patients treated with intermediate experimental doses of cytarabine (1g/m^2) alone or in association with other chemotherapeutic agents (meta-AMSA, daunorubicin, etoposide) developed diffuse interstitial pneumonia without a clear causal correlation with cytarabine.

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and a radiographically pronounced cardiomegaly has been reported following experimental high dose therapy with cytarabine used for the treatment of relapsed leukemia; fatal outcome has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local country requirements.

4.9 Overdose

No antidote exists for overdosage of CYTOSAR. Doses of 4.5 g/m^2 by intravenous infusion over 1 hour every 12 hours for 12 doses has caused an unacceptable increase in irreversible CNS toxicity and death. Interrupt the therapy and treat the resulting myelo-inhibition, including transfusions of whole blood or platelets and, if required, antibiotics.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimetabolite (pyrimidine analogue). ATC code: L01BC01

CYTOSAR (1-beta-D-arabinofuranosylcytosine) is a synthetic nucleotide that differs from the normal nucleotides, cytidine or deoxycytidine, for the substitution of ribose and deoxyribose with arabinose.

Cell cultures

Cytarabine is cytotoxic for a wide variety of proliferative mammalian cells in culture.

Mechanism of action

Its activity is phase specific and primarily directed at the cells in the S phase, during DNA synthesis.

Furthermore, in certain conditions it blocks the passage of the cells from the G_1 phase to the S phase. While the mechanism of action is not completely clear, it would appear that cytarabine acts by inhibiting DNA polymerase.
A limited but significant incorporation of cytarabine in both the DNA and the RNA has been reported. Cytarabine induces extensive chromosomal damage, including rupture of the chromatids and the neoplastic transformation of mouse cells in culture.

Deoxycytidine prevents or delays, but does not eliminate, the cytotoxic action of cytarabine. Cytarabine has shown antiviral activity in the cells in culture, but this has not been confirmed in the controlled clinical studies regarding herpes zoster and chickenpox.

Pharmacodynamic effects

Cytarabine is metabolised by deoxycytidine kinase and by other nucleotide kinases to form nucleotide triphosphate, a powerful inhibitor of DNA polymerase; it is inactivated by pymiridine-nucleoside-deaminase which transforms it into a non-cytotoxic uracil derivative. The ratio between the kinase and deaminase levels would appear to be an important factor in determining the sensitivity or the resistance of the cells to cytarabine.

In mice, cytarabine has proved more active in tumours with a high rate of proliferation. The efficacy, directly related to the therapeutic regimen, proves optimal when the administration, carried out with doses repeated at short intervals or by continuous infusion, ensures that the drug is in contact with the maximum number of neoplastic cells in the S phase. The best results have been obtained when the treatment cycles have been alternated with sufficiently long rest periods to permit adequate recovery of the baseline conditions.

5.2 Pharmacokinetic properties

CYTOSAR is metabolised rapidly and is not effective if administered orally since only 20% of the dose is absorbed by the gastrointestinal tract.

After rapid intravenous infusion of marked cytarabine, a biphasic elimination curve is seen, characterized by an initial distribution phase with a half-life of around 10 minutes, followed by a second phase of elimination with a half-life of 1-3 hours. Once distribution is complete, more than 80% of the radioactivity in the plasma can be attributed to 1-beta-D-arabinofuranosyluracil (ara-U), an inactive metabolite. Within 24 hours approximately 80% of the radioactivity administered is to be found in the urine, where 50% of it is excreted in the form of ara-U.

Relatively constant plasma levels can be reached by means of continuous intravenous infusion. After intramuscular or subcutaneous administration of marked cytarabine, the plasmatic peaks of radioactivity are reached in 20-60 minutes and they are considerably lower than those reached after intravenous administration.

After a single intravenous administration, the levels of cytarabine in the cerebral spinal fluid are lower than those in the plasma. One patient, however, after two hours of continuous intravenous infusion, showed levels in the cerebral spinal fluid equal to 40% of the plasmatic levels at the steady-state. After intrathecal administration the mean half-life is approximately two hours and follows a prime pattern. Since there are low levels of deaminase in the cerebral spinal fluid, there is little conversion to ara-U.

Immunosuppressive action

CYTOSAR can annul the immune responses in human beings with little or no toxicity. It has been demonstrated that there is suppression of both the primary and secondary antibody response to the tetanus toxin and the E.Coli antigen VI. CYTOSAR has also demonstrated the capacity to inhibit cell-mediated immune responses, such as delayed cutaneous hypersensitivity to dinitrochlorobenzene. It has not, on the other hand, shown any effect in the case of delayed hypersensitivity reactions already present.

Five days after intensive treatment with CYTOSAR, suppression of the immune response has been observed, revealed by the following parameters: passage of the macrophages into the skin windows; response of the circulating antibodies to primary antigen stimulation; lymphocyte blastogenesis with phytohaemagglutinin.

Some days after suspension of the therapy, there has been a rapid return to normality.

5.3 Preclinical safety data

The toxicity of cytarabine in laboratory animals, similarly to its activity, is influenced to a considerable extent by the regimen of administration.
After a single intra-peritoneal administration of the drug, the DL10 proves to be in excess of 6000 mg/m2, while after repeated administrations every 3 hours, divided up into 8 injections, the DL10 is found to be lower and corresponds to a total dose equivalent to 750 mg/m^2.

Similarly, although a total dose of 1920 mg/ m^2 administered in 12 injections at 6-hourly intervals was lethal for beagle dogs (severe bone marrow hypoplasia with liver and kidney damage), dogs treated with the same total dose divided up into 8 injections, again at 6-hourly intervals, survived with minimal manifestations of toxicity. The main alteration encountered in the surviving dogs was a raised transaminase level.

The major dose-limiting toxicity of cytarabine observed in all tested species is myelosuppression, manifested by megaloblastosis, reticulocytopenia, leukopenia, thrombocytopenia. Other target organs include liver, kidney, and brain.

Cytarabine is embryotoxic and teratogenic and produced peri- and postnatal toxicity in various species. No formal fertility studies have been reported however sperm head abnormalities were observed following cytarabine treatment in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (to regulate pH)
Sodium hydroxide (to regulate pH)
Each bottle of solvent contains: water for injectable preparations.

6.2 Incompatibilities

Drug Incompatibilities
Cytarabine is incompatible in solution with various drugs; the incompatibilities are directly related to various factors such as, for example, the concentration of the drugs, the diluents used, the pH of the solution and the temperature.

CYTOSAR is physically incompatible with: heparin, insulin, 5-fluorouracil, penicillins such as naficillin, oxacillin and penicillin G, methylprednisolone sodium succinate and vitamins of the B group.

6.3 Shelf life

- Do not use Cytosar after the expiry date which is stated on the carton/vial after EXP:. The expiry date refers to the last day of that month.
- On the basis of the results obtained and the parameters tested, the reconstituted solution with 0.9% Benzyl alcohol in Water for Injections as bacteriostatic solvent (BWFI), seems to be stable from a physical - chemical point of view up to:

  - 4 days in refrigerator
  - 24 hours at 30°C

6.4 Special precautions for storage

Storage condition of finished product: Do not store above 25°C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

CYTOSAR 100 mg/5 ml: One glass vial with butyl rubber stopper and aluminium crimp containing 100 mg of lyophilised powder + one 5 ml glass ampoule of solvent

CYTOSAR 500 mg/10 ml: One glass vial with butyl rubber stopper and aluminium crimp containing 500 mg of lyophilised powder + one 10 ml glass ampoule of solvent

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

Pfizer Italia S.r.l. - Via Isonzo, 71 - 04100 Latina

MANUFACTURED, PACKED & RELEASED BY

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8. DATE OF REVISION OF THE TEXT

February 2018