SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

CYTOSAR® 100 mg Powder for solution for injection

CYTOSAR® 500 mg Powder for solution for injection

Bacteriostatic water for injection plus benzyl alcohol 0,9 % m/v

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CYTOSAR 100 mg contains 100 mg cytarabine per vial.

CYTOSAR 500 mg contains 500 mg cytarabine per vial.

CYTOSAR is packed with Bacteriostatic water for injection plus benzyl alcohol 0,9 % m/v and must be reconstituted before use.

Sugar free.

Excipients with known effect

One 5 mL ampoule of Bacteriostatic water for injection plus benzyl alcohol 0,9 % m/v contains 45 mg benzyl alcohol.

One 10 mL ampoule of Bacteriostatic water for injection plus benzyl alcohol 0,9 % m/v contains 90 mg benzyl alcohol.

DO NOT USE THIS DILUENT CONTAINING BENZYL ALCOHOL FOR INTRATHECAL USE OR FOR HIGH DOSE THERAPY (see sections 4.3, 4.4 and 4.2).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

CYTOSAR is available as a freeze-dried preparation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CYTOSAR 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 (ALL) and chronic myelocytic leukaemia (CML) (blast phase).

CYTOSAR may be used alone or in combination with other antineoplastic medicines. It is more effective when used in combination therapy with other medicines.

Children with non-Hodgkin's lymphoma have benefited from a combination medication programme 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.

4.2 Posology and method of administration

CYTOSAR is not active orally. The schedule and method of administration varies with the programme of therapy to be used.

Thrombophlebitis has occurred at the site of injection or infusion and patients have noted pain and inflammation at subcutaneous injection sites.

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 programmes, 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.

Posology

Dosage schedules

Acute non-lymphocytic leukaemia – induction of remission in adults and children

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 programmes are modifications of induction programmes and in general, use similar schedules of medicine therapy as were used during induction. Most programmes 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.

Intrathecal CYTOSAR should not be used to treat focal leukaemic involvement of the central nervous system.

Combined chemotherapy or high dose therapy

Before instituting a programme of combined chemotherapy or high dose therapy, the medical practitioner should be familiar with the literature, adverse reactions, precautions, contraindications and warnings applicable to all the medicines involved in the programme.

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 medicines, 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 programme to treat non-Hodgkin's lymphoma in children.

Dosage modification

The dosage of CYTOSAR must be modified or suspended when signs of serious haematologic 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.

Method of administration

CYTOSAR may be given by intravenous infusion, injection, intrathecally or subcutaneously.

When preparing CYTOSAR for intrathecal use, do not use diluents containing benzyl alcohol (see section 4.4). Many medical practitioners reconstitute with preservative-free 0,9 % sodium chloride for injection and use immediately.

CYTOSAR given intrathecally may cause systemic toxicity and careful monitoring of the haemopoietic system is indicated. Modification of the anti-leukaemia therapy may be necessary

(see section 4.4 and section 4.8). When CYTOSAR is administered both intrathecally and intravenously within a few days, there is an increased risk of spinal cord toxicity.

If high dose therapy is used, do not use diluents containing benzyl alcohol (see section 6.6).

4.3 Contraindications

- Hypersensitivity to cytarabine or any of the excipients of CYTOSAR listed in section 6.1.
- CYTOSAR is contraindicated in patients with depressed bone marrow i.e. in platelet counts under 50 000 or a polymorphonuclear granulocyte count under 1 000/mm^3.
- Administration of live or live-attenuated vaccines (see section 4.4).
- Pregnancy and lactation (see section 4.6).
- Intrathecal use of the supplied diluent is contraindicated as it contains benzyl alcohol (see section 4.4).
- The supplied diluent should not be used in pre-term or full-term neonates because of the risk of severe toxicity including abnormal respiration (see section 4.4, Gasping syndrome).

4.4 Special warnings and precautions for use

General

Only medical practitioners 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 CYTOSAR. 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.

Before beginning treatment, the medical practitioner should be familiar with the following text.

Haematologic effects

CYTOSAR is a potent bone marrow suppressant; the severity depends on the dose of the medicine and schedule of administration. Therapy should be started cautiously in patients with pre-existing medicine-induced bone marrow suppression. Patients receiving CYTOSAR 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. 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/mm^3. Counts of formed elements in the peripheral blood may continue to fall after CYTOSAR is stopped and reach lowest values after medicine-free intervals of 12 to 24 days. When indicated, restart therapy when definite signs of marrow recovery appear. Patients whose medicine is withheld until “normal” peripheral blood values are attained may escape from control. 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).

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

Dose schedules

Severe and fatal cardiomyopathy, CNS, GI and pulmonary toxicity have been reported following CYTOSAR therapy, more so with high dose (2 - 3 g/m^2) schedules of CYTOSAR.

Other reactions include cerebral and cerebellar dysfunction (which may be irreversible), including personality changes, somnolence, convulsion and coma, severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis, leading to peritonitis, sepsis and liver abscess, pulmonary oedema, liver damage with increased hyperbilirubinaemia, bowel necrosis, and necrotising colitis.

Severe and fatal pulmonary toxicity, adult respiratory distress syndrome and pulmonary oedema have occurred, more so following high dose schedules with CYTOSAR therapy.

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary oedema and radiographically pronounced cardiomegaly has been reported following therapy with CYTOSAR, especially at high doses used for the treatment of relapsed leukaemia.

Cases of cardiomyopathy with subsequent death have been reported following CYTOSAR and cyclophosphamide therapy when used for stem cell transplant preparation. This may be schedule and dose dependent.
Ophthalmological toxicity including corneal toxicity and haemorrhagic conjunctivitis, which may be diminished by prophylaxis with a local corticosteroid eye drop.

Peripheral motor and sensory neuropathies after consolidation with CYTOSAR, daunorubicin, and asparaginase have occurred in adult patients with acute non-lymphocytic leukaemia (ANLL). Patients treated with CYTOSAR should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurological disorders.

Severe skin rash, leading to desquamation has been reported. Complete alopecia is very commonly seen with high dose CYTOSAR therapy.

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 medicine is infused.

Anti-emetic therapy should be given to reduce, and if possible, prevent nausea and vomiting, since once experienced, it may become a conditioned response, and may not respond to anti-emetics.

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 CYTOSAR in combination with other medicines. Patients have responded to nonoperative medical management. Delayed progressive ascending paralysis resulting in death has been reported in children with acute myelocytic leukaemia (AML) following intrathecal and intravenous CYTOSAR at conventional doses in combination with other medicines.

Hepatic and/or renal function

The human liver apparently detoxifies a substantial fraction of an administered dose of CYTOSAR. In particular, patients with renal or hepatic function impairment may have a higher likelihood of CNS toxicity after high dose treatment with CYTOSAR. Use CYTOSAR with caution and possibly at reduced doses in patients whose liver or kidney function is poor.

Periodic checks of bone marrow, liver and kidney functions should also be performed in patients receiving CYTOSAR.

Neurological

Cases of severe neurological adverse reactions that ranged from headache to paralysis, cerebellar syndrome, coma and stroke-like episodes have been reported mostly in juveniles and adolescents given intravenous CYTOSAR.

Tumour lysis syndrome

CYTOSAR may induce hyperuricaemia secondary to rapid lysis of neoplastic cells. The medical practitioner 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.

Pancreatitis

Acute pancreatitis has been reported to occur in patients being treated with CYTOSAR.

Immunosuppressant effects/increased susceptibility to infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicines including CYTOSAR may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving CYTOSAR (see section 4.3). Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Gasping syndrome

CYTOSAR does not contain benzyl alcohol as an excipient; however, benzyl alcohol is contained in the diluent co-packaged with the freeze-dried powder for injection. The preservative benzyl alcohol has been associated with serious adverse events, including the “gasping syndrome”, and death in paediatric patients. Although normal therapeutic doses of CYTOSAR ordinarily deliver low amounts of benzyl alcohol, the minimum amount of benzyl alcohol at which toxicity may occur is not known.

The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys' capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity (see section 4.6).

If CYTOSAR is used in high dose or as intrathecal therapy, do not use a diluent containing benzyl alcohol. The preservative-free 0,9 % sodium chloride can be used for reconstitution (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Digoxin

Decreases in steady-state plasma digoxin concentrations and renal digoxin excretion was observed in patients receiving digoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without CYTOSAR or procarbazine. Therefore, monitoring of plasma digoxin levels is indicated in patients receiving similar combination chemotherapy regimens.

Gentamicin and amikacin

An *in-vitro* interaction study between gentamicin and CYTOSAR showed a CYTOSAR related antagonism for the susceptibility of *K. pneumoniae* and *Pseudomonas aeruginosa* strains. This study suggests that in patients on CYTOSAR being treated with gentamicin for a *K. pneumoniae* infection, the lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

Fluorocytosine

Clinical evidence showed possible inhibition of fluorocytosine efficacy therapy with CYTOSAR. This may be due to potential competitive inhibition of its uptake.

Methotrexate

Intravenous CYTOSAR given concomitantly with intrathecal methotrexate increases the risk of severe neurological adverse reactions such as headache, paralysis, coma and stroke-like episodes (see section 4.4).

Combination therapy:

Hepatic dysfunction was associated with the combined use of CYTOSAR and daunorubicin.

Veno-occlusive disease was associated with combined thioguanine and CYTOSAR therapy.

Allopurinol, colchicine, probenecid or sulfinpyrazone may interact with CYSTOSAR.

Combinations containing any of the following medicines may also interact with CYTOSAR: Blood dyscrasia-causing medicines (increase in leukopenia and/or thrombocytopenic effects), bone marrow depressants or radiotherapy (additive bone marrow depression), cyclophosphamide (increased cardiomyopathy), killed vaccines (decreased response), live vaccines (replication of virus may be potentiated, increased side effects and decreased antibody response).

4.6 Fertility, pregnancy and lactation

CYTOSAR is contraindicated during pregnancy and lactation (see section 4.3).

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant and to use highly effective contraceptive methods while receiving CYTOSAR. If a woman's male partner is receiving CYTOSAR, the woman should use highly effective contraceptive methods as well. It is generally advised to continue using contraception up to 6 months following the last administered dose of CYTOSAR.

Pregnancy

CYTOSAR is known to be teratogenic in some animals.

In human pregnancies, congenital abnormalities have been reported, more so when the foetus has been exposed to systemic therapy with CYTOSAR during the first trimester. The risks in the second and third trimester are still present. These include upper and lower distal limb defects, and extremity and ear deformities. Enlarged spleens and Trisomy C chromosome abnormalities have been reported.

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

Any infant born to a mother exposed to CYTOSAR must be followed up for normal development.

Benzyl alcohol which is contained in the diluent can cross the placenta (see section 4.4).

Breastfeeding

Mothers receiving CYTOSAR must not breastfeed their infants.

4.7 Effects on ability to drive and use machines

Serious central nervous system and eye side effects may occur that make driving or using machinery dangerous. Patients and their caregivers must be informed of these dangers.

4.8 Undesirable effects

Blood and lymphatic system disorders

As CYTOSAR 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 is 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 days 15 – 24. Then there usually 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 usually occurs in the next 10 days.

Infections and infestations

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 medicines following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, moderate or severe and fatal.

Musculoskeletal and connective tissue disorders

The Cytarabine Syndrome:

A cytarabine syndrome is characterised by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs within 6 – 12 hours following administration of the medicine. 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 and the need for continuation of therapy with CYTOSAR should be considered.

Tabulated summary of adverse reactions

The following side effects have been reported. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to <1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); and frequency not known (post-marketing reports).

Table 1: Adverse events associated with conventional and high dose therapy

MedDRA system organ class	**Frequency**	**Side effect**
Infections and infestations	Very common	Sepsis, pneumonia, infection[a]
	Not known	Injection site cellulitis
Blood and lymphatic system disorders	Very common	Bone marrow failure, thrombocytopenia, anaemia, megaloblastic anaemia, leukopenia, decreased reticulocyte count
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]
Cardiac disorders	Not known	Pericarditis, sinus bradycardia
Vascular disorders	Not known	Thrombophebitis
Respiratory, thoracic and mediastinal disorders	Not known	Dyspnoea, oropharyngeal pain, interstitial lung oedema, acute respiratory distress syndrome (ARDS)
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	Abnormal hepatic function
	Not known	Jaundice
	Very common	Alopecia, rash

Skin and subcutaneous tissue disorders	Common	Skin ulcer
	Not known	Palmar-plantar erythrodysaesthesia syndrome, urticaria, pruritus, ephelides
Musculoskeletal, connective tissue and bone disorders	Very common	Cytarabine Syndrome (see above)
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	Abnormal bone marrow biopsy, abnormal blood smear test

[a] may be mild, but can be severe and at times fatal

[b] may occur with rash and may be haemorrhagic with high dose therapy

[c] pain and inflammation at subcutaneous injection site

The incidence of side effects is higher with continuous intravenous administration than with rapid intravenous injection.

Adverse reactions reported in association with high dose therapy are included in the following table (also see section 4.4).

Table 2: Adverse reactions associated with high dose therapy

MedDRA system organ class	**Frequency**	**Side effect**
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, keratitis
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

A diffuse interstitial pneumonitis has been reported.

Peripheral motor and sensory neuropathies have been reported (see section 4.4).

An increase in cardiomyopathy with subsequent death has been reported when used in combination with cyclophosphamide (see section 4.4).

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary oedema and a radiographically pronounced cardiomegaly has been reported following therapy with CYTOSAR in relapsed leukaemia. This may prove fatal.

Acute pancreatitis has been reported (see section 4.4).
Severe skin rash, leading to desquamation, has been reported. Complete alopecia may occur (see section 4.4).

Intrathecal use

The most frequently reported reactions after intrathecal administration were nausea, vomiting and fever. Paraplegia has been reported. Necrotising leuko-encephalopathy with or without convulsion has been reported; in some cases, patients had also been treated with intrathecal methotrexate and/or hydrocortisone, as well as by central nervous system radiation. Isolated neurotoxicity has been reported including blindness.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to

report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no antidote 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.

Cessation of therapy followed by management of ensuing bone marrow depression including whole blood platelet transfusion and antibiotics as required.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents

Cytarabine, a pyrimidine nucleoside analogue, is an antineoplastic medicine which inhibits the synthesis of deoxyribonucleic acid. *In vitro,* it also has antiviral and immunosuppressant properties. Detailed studies on the mechanism of cytotoxicity *in vitro* suggest that the primary action of cytarabine is inhibition of deoxycytidine synthesis, although inhibition of cytidylic kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytocidal actions.

5.2 Pharmacokinetic properties

Cytarabine is deaminated to arabinofuranosyl uracil in the liver and kidneys. After intravenous administration to humans, only 5,8 % of the administered dose is excreted unaltered in the urine within 12 – 24 hours; 90 % of the dose is excreted as the deaminated medicine. Cytarabine appears to be metabolised rapidly, primarily by the liver and perhaps by the kidney. After a single high intravenous dose, blood levels fall to unmeasurable levels within 15 minutes in most patients. Some patients have no demonstrable circulating cytarabine as early as 5 minutes after injection.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CYTOSAR 100 mg and 500 mg

Hydrochloric acid for pH adjustment

Sodium hydroxide for pH adjustment

Bacteriostatic water for injection plus benzyl alcohol 0,9 % m/v

Water for injection

Benzyl alcohol (0,9 % m/v)

6.2 Incompatibilities

CYTOSAR has been known to be physically incompatible with heparin, insulin, methotrexate, 5-fluorouracil, penicillins and methylprednisolone.

6.3 Shelf life

Powder for solution for injection

CYTOSAR 100 mg: 36 months

CYTOSAR 500 mg: 60 months

Stability in infusion solutions

CYTOSAR is stable for seven days at room temperature when admixed at 0,5 mg/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, CYTOSAR 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/500 mL 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.

6.4 Special precautions for storage

Store at room temperature between 15 °C and 30 °C.

Once reconstituted, store at room temperature between 15 °C and 30 °C and use within 48 hours.

Discard any solution in which a slight haze develops.

6.5 Nature and contents of container

CYTOSAR 100 mg: 100 mg vial plus 5 mL water for injection (with benzyl alcohol 0,9 % m/v).

CYTOSAR 500 mg: 500 mg vial plus 10 mL water for injection (with benzyl alcohol 0,9 % m/v).

CYTOSAR 100 mg and 500 mg are in multidose vials.

Bacteriostatic water for injection plus benzyl alcohol 0,9 % m/v is available in ampoules of 5 mL and 10 mL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 4 µg/mL is compatible in dextrose 5 % in water for 8 hours.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

Building 2, 1st Floor

Maxwell Office Park

Magwa Crescent

Waterfall City

Midrand

Gauteng

1685

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

CYTOSAR 100 mg: H2757 (Act 101/1965)

CYTOSAR 500 mg: T/26/47

Bacteriostatic water for injection plus benzyl alcohol 0,9 % m/v: H/34/60

9. DATE OF FIRST AUTHORISATION

CYTOSAR 100 mg: N/A (Old medicine)

CYTOSAR 500 mg: 18 November 1987

Bacteriostatic water for injection plus benzyl alcohol 0,9 % m/v: 20 October 1975

10. DATE OF REVISION OF THE TEXT

30 July 2025

NAMIBIA: S2

Cytosar 100 mg: Reg. No. 14/26/0432

Cytosar 500 mg: Reg. No. 90/26/001300

BOTSWANA: S2

Cytosar 100 mg: Reg. No. B9311955

Cytosar 500 mg: Reg. No. B9311960

Manufacturer: Latina Pharma S.p.A., Sermoneta (LT), Italy