SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cytosar® 1G.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cytarabine 1 G/Vial

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Induction and maintenance of remission in acute myelocytic leukemia of adults and children. Treatment of other leukemias.

4.2 Posology and method of administration

Cytarabine is not active orally. The schedule and method of administration vary with the program of therapy to be used. Cytarabine may be given by intravenous infusion or injection Thrombophlebitis has occurred at the site of drug infusion in some patients. In most instances, however, the drug has been well tolerated.

Patients can tolerate higher total doses when they receive the drug by rapid intravenous injection as compared with slow infusion. This phenomenon is related to the drug's rapid inactivation and brief exposure of susceptible normal and neoplastic cells to significant levels after rapid injection. Normal and neoplastic cells seem to respond in somewhat parallel fashion to these different modes of administration and no clear-cut clinical advantage has been demonstrated for either.

If high dose therapy is used, do not use a diluent containing benzyl alcohol.

Conventional dose: In the induction therapy of acute non-lymphocytic leukemia, the usual cytarabine dose in combination with other anti-cancer drugs is 100 mg/m2/day by continuous I.V. infusion (Days 1-7) or 100 mg/m2 I.V. every 12 hours (Days 1-7).

High dose: 2-3 g/m2 as an I.V. infusion over 1-3 hours given every 12 hours for 2-6 days with or without additional cancer chemotherapeutic agents.

The literature should be consulted for the current recommendations for use in leukemia and pediatric non-Hodgkin's lymphoma.

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 is also physically compatible with methotrexate.

Use in Children
Similar to use in adults.

4.3 Contraindications

Therapy with cytarabine should not be considered in patients with pre-existing drug-induced bone marrow suppression, unless the clinician feels that such management offers the most hopeful alternative for the patient. Cytarabine should not be used in the management of non-malignant disease, except for immunosuppression.
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General: Only physicians experienced in cancer chemotherapy should use cytarabine.

Warnings:
Haematologic Effects: Cytarabine is a potent bone marrow suppressant; the severity depends on the dose of the drug and the schedule of administration. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving this drug must be under close medical supervision and, during induction therapy, should have leucocyte and platelet counts performed daily. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood.

The main toxic effect of cytarabine is bone marrow suppression with leukopenia, thrombocytopenia, anaemia, megaloblastosis and reduced reticulocytes. Less serious toxicity includes nausea, vomiting, diarrhoea and abdominal pain, oral ulceration, and hepatic dysfunction (see section 4.8).

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.

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 cytarabine treatment. Anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of Cytarabine (see section 4.8).

High Dose Schedules: Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of Cytarabine) has been reported following some experimental high dose (2-3 g/m^2) schedules with Cytarabine. These reactions include reversible corneal toxicity; cerebral and cerebellar dysfunction, usually reversible; somnolence; convulsion; severe gastro-intestinal ulceration, including pneumatosis cystoides

intestinalis, leading to peritonitis; sepsis and liver abscess; and pulmonary oedema (see section 4.8).

Cytarabine has been shown to be carcinogenic in animals. The possibility of a similar effect should be borne in mind when designing the long-term management of the patient.

Precautions: Patients receiving Cytarabine must be monitored closely. Frequent platelet and leucocyte counts are mandatory. Suspend or modify therapy when drug-induced marrow depression has resulted in a platelet count under 50,000 or a polymorphonuclear granulocyte count under 1,000 per cubic mm. Counts of formed elements in the peripheral blood may continue to fall after the drug is stopped, and reach lowest values after drug-free intervals of 12 to 24 days. If indicated, restart therapy when definite signs of marrow recovery appear (on successive bone marrow studies). Patients whose drug is withheld until 'normal' peripheral blood values are attained may escape from control.

Peripheral motor and sensory neuropathies after consolidation with high doses of cytarabine, daunorubicin, and asparaginase have occurred in adult patients with acutenon lymphocytic leukemia. Patients treated with high doses of cytarabine should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders.

Severe and sometimes fatal pulmonary toxicity, sudden respiratory distress syndrome and pulmonary oedema have occurred following experimental high dose schedules with cytarabine therapy.

Cases of cardiomyopathy with subsequent death have been reported following experimental high dose cytarabine and cyclophosphamide therapy when used for bone marrow transplant preparation. This may be schedule dependent.

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

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 Function: 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 at reduced dose in patients whose liver function is poor.

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

Neurological: 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.

The safety of this drug for use in infants is not established.

Tumour Lysis Syndrome: Like other cytotoxic drugs, cytarabine may induce hyperuricaemia 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 pharmacological measures as may be necessary to control this problem.

Pancreatitis: Cases of pancreatitis have been observed with the induction of cytarabine.

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.

Excipient information
This medicinal product contains less than 1 mmol (23 mg) sodium in each vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

5-Fluorocytosine should not be administered with Cytarabine as the therapeutic efficacy of 5-Fluorocytosine has been shown to be abolished during such therapy.

Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyldigoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without Cytarabine or procarbazine. Steady-state plasma digitoxin concentrations 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 gentamicin and Cytarabine showed a Cytarabine related antagonism for the susceptibility of *K. pneumoniae* strains. In patients on Cytarabine being treated with gentamicin for a *K.pneumoniae* infection, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

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 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Cytarabine is known to be teratogenic in some animal species. The use of cytarabine in women who are or who may become pregnant should be undertaken only after due consideration of the potential benefits and hazards.

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 cytarabine should be apprised of the potential risk to the foetus and the advisability of pregnancy continuation. There is a definite, but considerably reduced risk if therapy is initiated during the second or third trimester. Although normal infants have been delivered to patients treated in all three trimesters of pregnancy, follow-up of such infants would be advisable.

Breast-feeding
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing

infants from cytarabine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

This product should not normally be administered to patients who are pregnant or to mothers who are breast-feeding.

4.7 Effects on ability to drive and use machines

Cytarabine has no effect on intellectual function or psychomotor performance. Nevertheless, patients receiving chemotherapy may have an impaired ability to drive or operate machinery and should be warned of the possibility and advised to avoid such tasks if so affected.

4.8 Undesirable effects

Summary of the safety profile (see also section 4.4)

Most frequent adverse reactions include nausea, vomiting, diarrhoea, fever, rash, anorexia, oral and anal inflammation or ulceration, and hepatic dysfunction.

Blood and lymphatic system disorders:
Because 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 dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

Infections and infestations:
Viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body, may 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 may be mild, but can be severe and at times fatal.

Musculoskeletal and connective tissue disorders:
A Cytarabine syndrome has been described. It is characterised by fever, myalgia, bone pain, occasionally 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 serious enough to warrant treatment, corticosteroids should be contemplated as well as continuation of therapy with cytarabine.

The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency. Frequencies are defined as: Very common (>10%), Common (>1%, ≤10%), Uncommon (>0.1%, ≤1%), Rare (>0.01%, ≤0.1%), and Frequency not known (cannot be estimated from available data).

Adverse Reactions Table

Infections and Infestations:	
Very common	Sepsis, pneumonia, infection[a]
Frequency not known	Injection site cellulitis, liver abscess
Blood and Lymphatic System Disorders:	
Very common	Bone marrow failure, thrombocytopenia, anaemia, anaemia megaloblastic, leukopenia, reticulocyte count decreased

Immune System Disorders:	
Frequency not known	Anaphylactic reaction, allergic oedema
Metabolism and Nutrition Disorders:	
Frequency not known	Decreased appetite
Nervous System Disorders:	
Frequency not known	Neurotoxicity, neuritis, dizziness, headache
Eye Disorders:	
Frequency not known	Conjunctivitis[b]
Cardiac Disorders:	
Frequency not known	Pericarditis, sinus bradycardia
Vascular Disorders:	
Frequency not known	Thrombophlebitis
Respiratory, Thoracic and Mediastinal Disorders:	
Frequency not known	Dyspnoea, oropharyngeal pain
Gastrointestinal Disorders:	
Very common	Stomatitis, mouth ulceration, anal ulcer, anal inflammation, diarrhoea, vomiting, nausea, abdominal pain
Frequency not known	Pancreatitis, oesophageal ulcer, oesophagitis
Hepatobiliary Disorders:	
Very common	Hepatic function abnormal
Frequency not known	Jaundice
Skin and Subcutaneous Tissue Disorders:	
Very common	Alopecia, rash
Common	Skin ulcer
Frequency not known	Palmar-plantar erythrodysaesthesia syndrome, urticaria, pruritus, ephelides
Musculoskeletal, Connective Tissue and Bone Disorders:	
Very common	Cytarabine syndrome
Renal and Urinary Disorders:	
Frequency not known	Renal impairment, urinary retention
General Disorders and Administration Site Conditions:	
Very common	Pyrexia
Frequency 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

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

Adverse Reactions Table (High Dose Therapy)

Infections and Infestations:	
Frequency not known	Liver abscess, sepsis
Psychiatric Disorders:	
Frequency not known	Personality change[a]
Nervous System Disorders:	
Very common	Cerebral disorder, cerebellar disorder, somnolence
Frequency not known	Coma, convulsion, peripheral motor neuropathy, peripheral sensory neuropathy
Eye Disorders:	
Very common	Corneal disorder
Cardiac Disorders:	
Frequency not known	Cardiomyopathy[b], sinus bradycardia
Respiratory, Thoracic and Mediastinal Disorders:	
Very common	Acute respiratory distress syndrome, pulmonary oedema
Gastrointestinal Disorders:	
Common	Necrotising colitis
Frequency not known	Gastrointestinal necrosis, gastrointestinal ulcer, pneumatosis intestinalis, peritonitis
Hepatobiliary Disorders:	
Frequency 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 without clear cause that may have been related to cytarabine was reported in patients treated with experimental intermediate doses of cytarabine ($1g/m^2$) with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, VP-16).

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary oedema 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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product .Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

4.9 Overdose

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

There is no antidote for overdosage of cytarabine. Doses of 4.5g/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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pyrimidine analogues, ATC Code: L01BC01

Cytarabine, a pyrimidine nucleoside analogue, is an antineoplastic agent which inhibits the synthesis of deoxyribonucleic acid. It also has antiviral and immunosuppressant properties. Detailed studies on the mechanism of cytotoxicity in vitro suggests 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 doses is excreted unaltered in urine within 12-24 hours, 90% of the dose is excreted as the deaminated product. Cytarabine appears to be metabolised rapidly, primarily by the liver and perhaps by the kidney. After single high intravenous doses, blood levels fall to unmeasurable levels within 15 minutes in most patients. Some patients have indemonstrable circulating drug as early as 5 minutes after injection.

5.3 Preclinical safety data

Cytarabine is embryotoxic and teratogenic when administered to rodents during the period of organogenesis at clinically relevant doses. It is reported that cytarabine causes developmental toxicity, including damage to the developing brain, when administered during the peri- and postnatal period. No formal fertility studies have been reported however sperm head abnormalities were observed following cytarabine treatment in mice.

Cytarabine is mutagenic and clastogenic and produced malignant transformation of rodent cells in vitro.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric Acid conc.

Sodium Hydroxide (disks)
Nitrogen
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in sections 4.2 and 6.3 .

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials

Stability in Infusion Solutions
Chemical and physical stability studies of cytarabine have demonstrated that cytarabine is stable for seven days at room temperature when admixed at 0.5 mg/ml in glass IV bottles and plastic IV 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 IV bottles and plastic IV bags, cytarabine is stable for seven days at room temperature, -20 degrees C, and 4 degrees C in 5% Dextrose Injection; 5% Dextrose in 0.2% Sodium Chloride Injection; and, in 0.9% Sodium Chloride Injection Solutions.
Cytarabine is stable at room temperature at a concentration of 2 mg/ml in the presence of KCl equivalent to 50 meg/500 ml in Dextrose 5% in water and 0.9% Sodium Chloride for up to eight days.
Cytarabine is also stable at room temperature and at refrigerated temperature (8 degrees C) at a concentration of 0.2-1.0 mg/ml in the presence of Sodium Bicarbonate equivalent to 50 meq/L in Dextrose 5% in Water or Dextrose 5% in 0.2% Sodium Chloride for seven days in Travenol glass bottles or Viaflex bags.
Cytarabine injection, and the infused solutions prepared therefrom, contain(s) no antimicrobial agents. Therefore, it is recommended that further dilution be effected immediately prior to use and infusion be commenced as soon as practicable after preparation of the admixture. Infusion should be completed within 24 hours of preparation and the residue discarded.

6.4 Special precautions for storage

Powder freeze dried for solution for injection: Store below 25°C

RECONSTITUTION
Cytarabine 1g vial is to be used for preparation of a solution for single dose administration.
Cytarabine sterile powder can be dissolved in water for injection, 0.9% sodium chloride or 5% glucose in water with or without preservative.
The maximum concentration that can be obtained after reconstitution with Cytarabine is 100mg/ml. In order to have a solution of exact 100mg/ml the following volume should be added:

ml to add	cytarabine
9.4 ml	1 g

6.5 Nature and contents of container

Vial glass type I, box of 1 vial

6.6 Special precautions for disposal and other handling

IMPORTANT
No ampoule file is needed to open the ampoules. The neck of the ampoule is prescored at the point of constriction. A coloured dot on the ampoule head 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.

Cytarabine 1g vial is to be used for preparation of a solution for single dose administration

7. LICENSE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725, Israel

8. LICENSE NUMBER

057-70-27036

Revised in January 2022 according to MOHs guidelines