PROPOSED PROFESSIONAL INFORMATION (PI)

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CYTARABINE 100 mg/1 mL FRESENIUS

CYTARABINE 500 mg/5 mL FRESENIUS

CYTARABINE 1 g/10 mL FRESENIUS

CYTARABINE 2 g/20 mL FRESENIUS

Pharmaceutical form

Solution for infusion or injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of solution contains 100 mg of cytarabine.

CYTARABINE 100 mg/1 mL FRESENIUS: Each 1 mL vial contains 100 mg of cytarabine.

CYTARABINE 500 mg/5 mL FRESENIUS: Each 5 mL vial contains 500 mg of cytarabine.

CYTARABINE 1 g/10 mL FRESENIUS: Each 10 mL vial contains 1 g of cytarabine.

CYTARABINE 2 g/20 mL FRESENIUS: Each 20 mL vial contains 2 g of cytarabine.

Excipients:

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion.

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CYTARABINE FRESENIUS 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).

CYTARABINE FRESENIUS 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 program that included cytarabine, as contained in **CYTARABINE FRESENIUS**.

CYTARABINE FRESENIUS 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

"CYTARABINE FRESENIUS should only be prescribed by a medical practitioner experienced in the utilisation of antineoplastic medicines."

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, cytarabine as contained in **CYTARABINE FRESENIUS** 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:

CYTARABINE FRESENIUS – 100 mg/m^2 per 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.

Combined chemotherapy or high dose therapy:

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

High-dose therapy:

CYTARABINE FRESENIUS, 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:

Cytarabine, as contained in **CYTARABINE FRESENIUS** has been used as part of a multi-medicine

program to treat non-Hodgkin's lymphoma in children.

Dosage modification:

The dosage of **CYTARABINE FRESENIUS** 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.

Special populations

Paediatric patients:

Safety in infants has not been established.

Patients with hepatic and renal impairment:

Patients with impaired hepatic or renal function: Dosage should be reduced.

Method of administration

CYTARABINE FRESENIUS is not active orally. The schedule and method of administration varies with the program of therapy to be used. **CYTARABINE FRESENIUS** may be given by intravenous infusion, injection or subcutaneously.

CYTARABINE FRESENIUS is NOT recommended for intrathecal use.

“For precautions to be taken before handling or administering **CYTARABINE FRESENIUS**, and instructions for dilution, see section 6.6.”

4.3 Contraindications

Therapy with **CYTARABINE FRESENIUS** is contraindicated in patients with depressed bone marrow. Hypersensitivity to **cytarabine** or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

1. General: Only medical practitioners experienced in cancer chemotherapy should use CYTARABINE FRESENIUS.

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 medicine.

Haematologic Effects:

Cytarabine, such as in **CYTARABINE FRESENIUS**, is a potent bone marrow suppressant; the severity depends on the dose of the medicine and the schedule of administration. Patients receiving **CYTARABINE FRESENIUS** must be monitored closely. Daily haemoglobin testing, platelet and leucocyte counts, and frequent bone marrow examination are mandatory. Suspend or modify 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. 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 defenses, 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 cardiac, CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following 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 as found in **CYTARABINE FRESENIUS** 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.

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 high doses of **CYTARABINE FRESENIUS** should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders.

Severe and sometimes fatal pulmonary toxicity, adult respiratory distress syndrome and pulmonary oedema have occurred following experimental high dose schedules with cytarabine, as found in **CYTARABINE FRESENIUS** therapy.

Cases of cardiomyopathy with subsequent death have been reported following experimental high dose cytarabine, as found in **CYTARABINE FRESENIUS** 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 medicine 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 medicines. Patients have responded to

non-operative 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 medicines.

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 **CYTARABINE FRESENIUS** 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 FRESENIUS**.
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 **CYTARABINE FRESENIUS** for use in infants is not established.

Tumour Lysis Syndrome: As a cytotoxic medicine, **CYTARABINE FRESENIUS** 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, as found in **CYTARABINE FRESENIUS**.

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.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

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.

5-fluorocytosine: 5-Fluorocytosine should not be administered with cytarabine as the therapeutic efficacy of 5-Fluorocytosine has been shown to be abolished during such therapy. The inhibition of efficacy of fluorocytosine, may be ascribed to potential competitive inhibition of its uptake.

Digoxin: 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, as found in **CYTARABINE FRESENIUS** 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.

Gentamicin: 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 FRESENIUS** 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 FRESENIUS** 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).

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.

4.6 Fertility, pregnancy and lactation

Women of Childbearing potential

Men and women have to use effective contraception during and up to 6 months after treatment.

Pregnancy:

CYTARABINE FRESENIUS 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, haematocrit or platelets, electrolyte abnormalities, eosinophilia, increased lgM levels, and hyperpyrexia possibly due to sepsis.

Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, 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.

Lactation

Safety in lactation has not been established. Patients on **CYTARABINE FRESENIUS** should not breastfeed.

Fertility:

Fertility studies to assess the reproductive toxicity of cytarabine have not been formally conducted. Given that cytarabine has a mutagenic potential which could induce chromosomal damage in the

human spermatozoa (see section 4.8), males undergoing cytarabine treatment, and their partner should be advised to use a reliable contraceptive method during and up to 6 months after treatment.

4.7 Effects on ability to drive and use machines

Patients receiving **CYTARABINE FRESENIUS** 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 FRESENIUS** 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 FRESENIUS** alone or in combination with other immunosuppressive medicines 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

The Cytarabine (Ara-C) Syndrome:

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 medicine 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 FRESENIUS.**

The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency.

Adverse Reactions Table

Adverse Reactions Table	
Infections and Infestations:	
Frequent	Sepsis, pneumonia, infection[a]
Frequency not known	Injection site cellulitis, liver abscess
Blood and Lymphatic System Disorders:	
Frequent	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:	
Frequent	Thrombophlebitis, bleeding
Respiratory, Thoracic and Mediastinal Disorders:	
Frequency not known	Dyspnoea, oropharyngeal pain
Gastrointestinal Disorders:	

Adverse Reactions Table	
Frequent	Stomatitis, mouth ulceration, anal ulcer, anal inflammation, diarrhoea, vomiting, nausea, abdominal pain
Frequency not known	Pancreatitis, oesophageal ulcer, oesophagitis
Hepatobiliary Disorders:	
Frequent	Hepatic function abnormal
Frequency not known	Jaundice
Skin and Subcutaneous Tissue Disorders:	
Frequent	Alopecia, rash, skin ulcer
Frequency not known	Palmar-plantar erythrodysaesthesia syndrome, urticaria, pruritus, ephelides
Musculoskeletal, Connective Tissue and Bone Disorders:	
Frequent	Cytarabine syndrome
Renal and Urinary Disorders:	
Frequency not known	Renal impairment, urinary retention
General Disorders and Administration Site Conditions:	
Frequent	Pyrexia
Frequency not known	Chest pain, injection site reaction[c]
Investigations:	
Frequent	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 haemorrhagic 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:	
Frequent	Cerebral disorder, cerebellar disorder, somnolence
Frequency not known	Coma, convulsion, peripheral motor neuropathy, peripheral sensory neuropathy
Eye Disorders:	
Frequent	Corneal disorder
Cardiac Disorders:	
Frequency not known	Cardiomyopathy[b], sinus bradycardia
Respiratory, Thoracic and Mediastinal Disorders:	
Frequent	Acute respiratory distress syndrome, pulmonary oedema
Gastrointestinal Disorders:	
Frequent	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:	
Frequent	Skin exfoliation
[a]personality change was reported in association with cerebral and cerebellar dysfunction. [b]with subsequent death	

Other adverse reactions

Other adverse reactions include: chest pains, pericarditis and freckling.

A diffuse interstitial pneumonitis without clear cause that may have been related to cytarabine, as found in **CYTARABINE FRESENIUS**, was reported in patients treated with experimental intermediate doses of cytarabine (1 g/m^2) with and without other chemotherapeutic medicines (meta-MASA, daunorubicin, VP-16).

Additional adverse effects with high dose schedules of cytarabine

Severe and fatal central nervous system, gastro-intestinal and pulmonary toxicity, different from that seen with conventional therapy regimens of cytarabine has been reported following high dose (2 – 3 g/m^2) schedules of cytarabine These reactions include corneal toxicity, and haemorrhagic 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 cytarabine in combination therapy.

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 leukaemia; fatal outcome has been reported.

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 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.

Intrathecal use

Cytarabine is not recommended for intrathecal use; as the following side-effects have been reported with such use: systemic reactions: bone marrow depression, nausea, vomiting. Occasionally, severe spinal cord toxicity even leading to quadriplegia and paralysis, necrotising encephalopathy, with or

without convulsion, blindness and other isolated neurotoxicities have been reported.

Carcinogenesis, mutagenesis, impairment of fertility

Extensive chromosomal damage, including chromatid breaks has been produced by cytarabine, and malignant transformation of rodent cells in culture has been reported.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Symptoms

"The major toxicity with therapeutic doses are reversible bone marrow suppression, corneal, cerebral and cerebellar dysfunction."

Doses of 4,5 g/m^2 by IV infusion over one hour every 12 hours for 12 doses has caused an unacceptable increase in irreversible CNS toxicity and death.

Treatment:

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

There is no specific antidote **for CYTARABINE FRESENIUS overdosage.**

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: /Class of medicine: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, pyrimidine analogue

ATC code: L01BC01

Mechanism of action

Cytarabine, a pyrimidine nucleoside analogue, is an antineoplastic medicine which inhibits the synthesis of deoxyribonucleic acid. It also has 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. **CYTARABINE FRESENIUS** has been reported to cause chromosome breaks *in-vitro*.

5.2 Pharmacokinetic properties

Cytarabine is deaminated to the inactive metabolite, 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 arabinofuranosyl uracil. 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 medicine 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

Sodium Hydroxide

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

18 months

After first opening, the product should be used immediately.

6.4 Special precautions for storage

Store between 15 °C to 25 °C. Do not refrigerate or freeze.

For storage conditions, see section 6.3.

6.5 Nature and contents of container

CYTARABINE 100 mg/1 mL FRESENIUS:

Solution for injection is filled in 2 mL Type I, colourless glass vial closed with grey bromobutyl rubber stopper, and sealed with green aluminium flip off overseal.

CYTARABINE 500 mg/5 mL FRESENIUS:

Solution for injection is filled in 5 mL Type I, colourless glass vial closed with grey bromobutyl rubber stopper, and sealed with blue aluminium flip off overseal.

CYTARABINE 1 g/10 mL FRESENIUS:

Solution for injection is filled in 10 mL Type I, colourless glass vial closed with grey bromobutyl rubber stopper, and sealed with red aluminium flip off overseal.

CYTARABINE 2 g/20 mL FRESENIUS:

Solution for injection is filled in 20 mL Type I, colourless glass vial closed with grey bromobutyl rubber

stopper, and sealed with yellow aluminium flip off overseal.

The package contains 1 vial of 1 mL, 5 mL, 10 mL and 20 mL, respectively.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Prior to use, vials **CYTARABINE FRESENIUS** must be warmed to 55 °C, for 30 minutes, with adequate shaking, and allowed to cool to room temperature.

Once opened, the contents of each vial must be used immediately and not stored.

Discard any unused portion.

Water for injections, 0,9 % saline or 5 % dextrose are commonly used infusion fluids for **CYTARABINE FRESENIUS**. Compatibility must be assured before mixing with any other substance.

Infusion fluids containing **CYTARABINE FRESENIUS** should be used immediately (see section 6.3).

Disposal and Spills: To destroy, place in a high risk (for cytotoxics) waste disposal bag and incinerate at 1100 °C. If spills occur, restrict access to the affected area and adequate protection including gloves and safety gloves and safety spectacles should be worn. Limit the spread and clean the area with absorbent paper/material. Spills may also be treated with 5 % sodium hypochlorite. The spill area should be cleaned with copious amounts of water. Place the contaminated material in a leak proof disposal bag for cytotoxics and incinerate at 1100 °C.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Limited

Stand 7, Growthpoint Business Park

162 Tonetti Street, Halfway House Extension 7

Midrand, Gauteng, 1685

Telephone number: (011) 545 0000

8 REGISTRATION NUMBER(S)

CYTARABINE 100 mg/1 mL FRESENIUS: 49/26/0043

CYTARABINE 500 mg/5 mL FRESENIUS: 49/26/0044

CYTARABINE 1 g/10 mL FRESENIUS: 49/26/0045

CYTARABINE 2 g/20 mL FRESENIUS: 49/26/0046

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 May 2021

10 DATE OF REVISION OF THE TEXT

17 November 2025