SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cytarabine 100 mg/ml solution for injection or infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 100 mg of cytarabine.

Each 1 ml vial contains 100 mg of cytarabine.

Each 5 ml vial contains 500 mg of cytarabine.

Each 10 ml vial contains 1 g of cytarabine.

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’.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion.

clear, colourless solution.

pH- 7.0 - 9.5

Osmolarity: 250 to 400 mOsm/L

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cytotoxic. For induction of remission in acute myeloid leukaemia in adults and for other acute leukaemias of adults and children.

4.2 Posology and method of administration

By intravenous infusion or injection or subcutaneous injection.

Only general recommendations can be given, as acute leukaemia is almost exclusively treated with combinations of cytostatics.

Dosage recommendation may be converted from those in terms of bodyweight to those related to surface area by means of nomograms.

1) Remission induction: Adult

a) Continuous treatment:

i) Rapid injection **- 2 mg/kg/day** is a judicious starting dose. Administer for 10 days. Obtain daily blood counts. If no antileukaemic effect is noted and there is no apparent toxicity, increase to **4 mg/kg/day** and maintain until therapeutic response or toxicity is evident. Almost all patients can be carried to toxicity with these doses.

ii) **0.5-1.0 mg/kg/day** may be given in an infusion of up to 24 hours duration. Results from one-hour infusions have been satisfactory in the majority of patients. After 10 days this initial daily dose may be increased to **2 mg/kg/day** subject to toxicity. Continue to toxicity or until remission occurs.

b) Intermittent treatment:

i) **3-5 mg/kg/day** are administered intravenously on each of five consecutive days. After a two to nine day rest period, a further course is given. Continue until response or toxicity occurs.

The first evidence of marrow improvement has been reported to occur 7-64 days (mean 28 days) after the beginning of therapy.

In general, if a patient shows neither toxicity nor remission after a fair trial, the cautious administration of higher doses is warranted. As a rule, patients have been seen to tolerate higher doses when given by rapid intravenous injection as compared with slow infusion. This difference is due to the rapid metabolism of Cytarabine and the consequent short duration of action of the high dose.

2) Maintenance therapy:

Remissions which have been induced by cytarabine, or by other drugs, may be maintained by intravenous or subcutaneous injection of 1 mg/kg once or twice weekly.

Paediatric population:

Children appear to tolerate higher doses of cytarabine than adults, and where the range of doses is given, children should receive the higher dose.

Patients with hepatic and renal impairment:

Patients with impaired hepatic or renal function: Dosage should be reduced (see section 4.4).

Cytarabine can be dialyzed. Therefore, Cytarabine should not be administered immediately before or after a dialysis.

Elderly Patients:

There is no information to suggest that a change in dosage is warranted in the elderly. Nevertheless, the elderly patient does not tolerate drug toxicity as well as the younger patient, and particular attention should thus be given to drug induced leukopenia, thrombocytopenia, and anaemia, with appropriate initiation of supportive therapy when indicated.

4.3 Contraindications

Therapy with cytarabine should not be considered in patients with severe bone marrow suppression. 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

Degenerative and toxic encephalopathies, especially after the use of methotrexate or treatment with ionising radiation

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, hemoglobin 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/m2 to 600 mg/m2, 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/m2) 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 hemoglobin, 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 acute non 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, adult respiratory distress syndrome and pulmonary oedema have occurred following experimental high dose schedules with cytarabine therapy.

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.

High-dose: The risk of CNS side effects is higher in patients who have previously had CNS treatment as chemotherapy intrathecally or radiation therapy.

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

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 medicinal products and other forms of interaction

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.

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

Breast-feeding:

Cytarabine should not be administered to mothers who are 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.

Fertility:

No formal fertility studies have been reported however sperm head abnormalities were observed following cytarabine treatment in mice.

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 using the following convention:

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)
Not known (cannot be estimated from the 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:	
Common	Hyperuricaemia
Frequency not known	Decreased appetite
Nervous System Disorders:	
Frequency not known	Neurotoxicity, neuritis, dizziness, headache
Eye Disorders:	
Frequency not known	Conjunctivitis[b]
Cardiac Disorders:	
Very rare	Arrhythmia
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
Common	Dysphagia
Uncommon	Pneumatosis cystoides intestinalis, necrotising colitis, peritonitis
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

Adverse Reactions Table	
Common	Skin ulcer
Very rare	Neurophilic eccrine hidradenitis
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]
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

Adverse Reactions Table (High Dose Therapy)	
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 hemotherapeutic 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.

Nervous system disorders:
After treatment with high doses of cytarabine, symptoms of cerebral or cerebellar influence like personality changes, affected alertness, dysarthria, ataxia, tremor, nystagmus, headache, confusion, somnolence, dizziness, coma, convulsions, etc. appear in 8-37 % of treated patients. The incidence in elderly (>55 years) may be even higher. Other predisposing factors are impaired liver and renal function, previous CNS treatment (e.g., radiotherapy) and alcohol abuse. CNS disturbances are in the most cases reversible.

The risk of CNS toxicity increases if the cytarabine treatment - given as high dose i.v.- combined with another CNS toxic treatment such as radiation therapy or high dose.

Gastrointestinal disorders:
Especially in treatment with high doses of cytarabine, more severe reactions may appear in addition to common symptoms. Intestinal perforation or necrosis with ileus and peritonitis have been reported.
Liver abscesses, hepatomegaly, Budd-Chiari-syndrome (hepatic venous thrombosis) and pancreatitis have been observed after high-dose therapy.

Others
Following cytarabine high-dose therapy, rhabdomyolysis, amenorrhoea and azoospermia have been reported.

Intrathecal use
Cytarabine is not recommended for intrathecal use; however, the following side-effects have been reported with such use. Expected 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.

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. Healthcare professionals are asked to report any suspected adverse reactions in the UK via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

No specific antidote. Managed advised at overdosage include: Cessation of therapy, followed by management of ensuing bone marrow depression including whole blood or platelet transfusion and antibiotics as required. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, pyrimidine analogue

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.

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The half life of the drug is 10 minutes.

High dose cytarabine achieves plasma peak levels 200 fold higher than that observed with conventional dose regimen. The peak of inactive metabolite ARA-U , with high dose regimen, is observed after only 15 minutes. The renal clearance is slower with high dose cytarabine than with conventional dose cytarabine. The cerebrospinal fluid (CSF) levels achieved , after high dose 1-3g/m^2 cytarabine intravenous infusion, are around 100-300 nanograms/ml.

Peak plasma levels are achieved about 20-60 minutes after subcutaneous application. At comparable doses, they are significantly lower than the plasma levels achieved after intravenous administration.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric Acid (for pH-adjustment)

Sodium Hydroxide (for pH-adjustment)

Water for injections

6.2 Incompatibilities

Solutions of Cytarabine have been reported to be incompatible with various drugs, i.e. carbenicillin sodium, cephalothin sodium, fluorouracil, gentamicin sulphate, heparin sodium, hydrocortisone sodium succinate, insulinregular, methylprednisolone sodium succinate, nafacillin sodium, oxacillin sodium, penicillin G sodium (benzylpenicillin), methotrexate, prednisolone succinate.

However, the incompatibility depends on several factors (e.g. concentrations of the drug, specific diluents used, resulting pH, temperature). Specialised references should be consulted for specific compatibility information.

This medicinal product must not be mixed with other medicinal products excepts those mentioned in section 6.6.

6.3 Shelf life

18 months

After first opening:

After first opening, product should be used immediately.

Shelf life after dilution:

After dilution, chemical and physical in-use stability has been demonstrated for 8 days below 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store between 15 degrees C and 25 degrees C. Do not refrigerate or freeze.

For storage conditions after first opening and after the dilution of the medical product, see section 6.3.

6.5 Nature and contents of container

For 1 ml,

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

For 5 ml,

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

For 10 ml,

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

For 20 ml,

Solution for injection is filled in 20 ml Type - I colourless glass vial closed with 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

For single use only.

Cytarabine is intended for intravenous or subcutaneous use only.

The diluted solution should be clear, colourless solution free, from visible particles.

Parenteral drugs should be inspected visually for particulate matter and discolouration, prior to administration, whenever solution and container permit.

If the solution appears discoloured or contains visible particles, it should be discarded.

Cytarabine injection can be diluted with sterile water for injections, glucose intravenous infusion (5 % w/v) or sodium chloride intravenous infusion (0.9 % w/v).

The dilution compatibility study has been carried out in polyolefin infusion bags.

The concentration over which the physico-chemical stability of cytarabine has been demonstrated is 0.04 - 4 mg/ml.

If crystallization is observed as a result of exposure to low temperatures, redissolve the crystals by warming up to 55°C for no longer than 30 minutes and shake until the crystals are dissolved. Allow to cool to room temperature before use.

Once opened, the contents of each vial must be used immediately and not stored.
Infusion fluids containing cytarabine should be used immediately.

Cytotoxic Handling Guidelines

Administration:

Should be administered by, or under the direct supervision of, a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Preparation (Guidelines):

1. Chemotherapeutic agents should be prepared for administration only by professionals trained in the safe use of the preparation.

2. Operations such as dilution and transfer to syringes should be carried out only in the designated area.

3. The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.

4. Pregnant personnel are advised not to handle chemotherapeutic agents.

Contamination:

(a) In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of skin. Medical advice should be sought if the eyes are affected.

(b) In the event of spillage, operators should put on gloves and mop up the spilled material with a sponge kept in the area for that purpose. Rinse the area twice with water. Put all solutions and sponges into a plastic bag and seal it.

Disposal:

Syringes, container, absorbent materials, solution and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated at 1100oC.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Ltd.

Cestrian Court

Eastgate Way, Manor Park

Runcorn, Cheshire, WA7 1NT

United Kingdon

8 MARKETING AUTHORISATION NUMBER(S)

PL 08828/0301

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/06/2012

10 DATE OF REVISION OF THE TEXT

14/01/2021