Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cytarabine Ebewe 50mg/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml solution for injection or infusion contains 50 mg Cytarabine
Each 10ml solution for injection or infusion contains 500 mg Cytarabine
Each 20ml solution for injection or infusion contains 1000 mg Cytarabine
Each 40ml solution for injection or infusion contains 2000 mg Cytarabine

Excipients:
This medicinal product contains 2.14mg of sodium in 1ml of solution.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion

Clear, colourless sterile solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cytarabine can be used alone or in combination for induction of remission and/or maintenance therapy in patients with acute myeloid leukaemia, acute non-lymphoplastic leukaemias, erythroleukaemia, blast crises of chronic myeloid leukaemia.

4.2 Posology and method of administration

Posology

Cytarabine “Ebewe” can be diluted with water for injection BP, Glucose intravenous infusion BP or sodium chloride intravenous infusion BP.

Method of administration

May be administered intravenously (IV) or subcutaneously (SC) only.

The product is hypertonic and must not be administered by the intrathecal route.

The following doses are given as a guide, but the clinician should consult relevant protocols for the appropriate dosage of cytarabine and other antineoplastic agents given in combination. Most doses are given in mg/kg but may be converted to doses related to surface area by the use of standard nomograms.

Remission Induction (Adults):
Continuous Dosing: The usual dose in leukaemia is 2 mg/kg by rapid intravenous injection daily for ten days. If after ten days neither therapeutic response nor toxicity has been observed, the dose may be increased to 4mg/kg until a therapeutic response or toxicity is evident. Daily blood counts should be taken. Almost all patients can be carried to toxicity with these doses.

Alternatively, 0.5 to 1 mg/mg may be infused daily in 1-24 hours for ten days, and then at a rate of 2 mg/kg/day until toxicity is observed. Continue to toxicity or until remission occurs. Results for one hour infusions have been satisfactory in the majority of patients.

Intermittent dosing: Cytarabine may be given as intermittent IV doses of 3-5 mg/kg daily, for five consecutive days. This course of treatment can be repeated after an interval of 2 to 9 days, and repeated until the therapeutic response or toxicity is exhibited.

Evidence of bone marrow improvement has been reported to occur 7-64 days after the beginning of therapy.

In general, if a patient shows neither remission nor toxicity after a trial period, then cautiously administered higher doses can be administered. Generally, patients tolerate higher doses given by rapid intravenous injection rather than slow infusion.

As a single agent for induction of remission in patients it acute leukaemia, cytarabine have been given in doses of 200 mg/m2 by continuous IV infusion for five days at approximately 2 week intervals.

Maintenance Therapy: to maintain remission, doses of 1-1.5 mg/kg may be given intravenously or subcutaneously, once or twice weekly.

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

Elderly: No data is available to suggest that a change in dose is necessary in the elderly. However, the elderly patient is more susceptible to toxic reactions and therefore particular attention should be paid to the drug induced leucopenia, thrombocytopenia and anaemia.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Patients who have already received a drug which can induce bone marrow suppression should not be treated with Cytarabine, unless the clinician deems such a treatment to be vitally important to the patient.

Anaemia, leucopenia and thrombocsytopenia of non-malignant etiology (e.g. bone marrow aplasia), unless the benefits outweigh the risk.

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

Hypersensitivity to cytarabine or of one of the other ingredients.
The management of non-malignant disease except for immunosuppression.
During pregnancy, cytarabine should only be administered on strict indication, where the benefits of the drug to the mother should be weighed against possible hazards to the foetus (see section 4.6)

4.4 Special warnings and precautions for use

Cytarabine should only be used with great caution in patients who have recently received radiotherapy or other cytotoxic agents.

Cytarabine should only be administered with caution under the direction of a specialist oncology service having the facilities for regular monitoring of clinical biochemical and haematological effects during and after administration.

Cytarabine is a cytotoxic product. Patients treated with Cytarabine must therefore be kept under strict supervision.

Rapid intravenous doses are gastro-intestinally better tolerated than slow intravenous infusions.

In view of the fact that the product is to a large extent broken down in the liver, the drug must be administered with extreme caution and in a low dosage to patients with liver function disorders.

Cytarabine must not be administered to patients with acute and/or serious infections.

Cytarabine has been shown to be mutagenic and carcinogenic in animals. The possibility of the above effects should be considered when cytarabine is used in long-term management of patients. Both male and female patients who are sexually mature must take contraceptive measures during and until six months after the therapy with Cytarabine (See section 4.6).

No effects have been observed as a result of exposure during handling. Slight irritation of the eye is possible. Repeated or continuous contact with the skin can lead to irritation. After accidental contact, wash the area of skin with copious amounts of water and soap.

Each treatment of a patient with acute leukaemia will unavoidably result in a more or less serious - but temporary - bone marrow depression. Monitoring of the number of platelets and granulocytes in the blood is necessary to determine whether support treatment is necessary. The effect of the treatment is determined by measuring the number of leukaemic blast cells in the blood and bone marrow.

Cytarabine is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving the drug must be kept under close medical supervision. Leucocyte and platelet counts should be performed frequently and daily during induction. Periodic bone marrow examinations should be conducted; the examinations should be frequent after blast cells have disappeared from the peripheral blood. Facilities should be available for management of complications of possibly fatal bone marrow suppression (infection resulting from granulocytopenia and other impaired body defences and haemorrhage secondary tothrombocytopenia).

Therapy should be suspended or modified when drug-induced bone marrow depression results in a platelet count of less than 50,000 or a polymorphonuclear count of under 1000 per cubic mm. Counts may continue to fall after the therapy has been discontinued and may reach lowest values after five to seven days. Therapy may be restarted when the bone marrow appears to be recovering on successive bone marrow studies. Therapy should not wait until the normal blood values are obtained to be re-initiated. . If treatment is not resumed before blood values return to normal, the disease can get out of control. One case of anaphylaxis that resulted in acute cardiopulmonary arrest and necessitated resuscitation has been reported.

Periodic determinations of renal and hepatic functions should be performed, and the drug should be used with caution and at reduced dosages in patients with impaired hepatic function. However, dosage reduction does not appear to be necessary in patients with impaired renal function. The human liver apparently detoxifies a substantial fraction of the administered dose.

Concurrent granulocyte-transfusion should be avoided as severe respiratory insufficiency has been reported.

Hyperuricaemia prophylaxis is concurrently essential.

Cytarabine can lead to increased uric acid levels in the blood, as a result of a lysis of the neoplastic cells. Regular monitoring of the uric acid levels in the blood is therefore recommended. If necessary, supporting and pharmacological measures should be taken to get hyperuricaemia under control. In the case of patients with a high number of blast cells or large tumour masses (non-Hodgkin’s lymphomas) prophylaxis of hyperuricaemia is required.

In addition to the predictable haematological toxicity, in some cases serious or life-threatening side effects can occur to the CNS, the gastrointestinal tract or the lungs.

Patients with gastrointestinal ulcers, or who have recently had an operation must be kept under close observation for indications which point to haemorrhaging, and if necessary platelets must be administered by transfusion, as required.

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.

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 intravenous cytarabine at conventional doses in combination with other drugs.

High dose therapy
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 doeses of cytarabine should be observed for neuropathy since dose adjustments may be needed to avoid irreversible neurologic disorders

High-dose cytarabine toxicities:
The toxicity of high dose cytarabine can be more severe than the toxicity of normal dose of cytarabine, and may include cerebellar and cerebral toxicity, conjunctivitis (make sure the patient is on steroid eye drops during therapy), corneal keratitis, exanthema, hyperbilirubinaemia, liver damage, GI perforation, pancreatitis, pulmonary oedema, pericarditis, and tamponade.
Cytarabine has been shown to be mutagenic and carcinogenic in animals. The possibility of the above effects should be considered when cytarabine is used in long-term management of patients.

The risk of CNS toxicity increases if high dose cytarabine is given in combination with another CCNS toxic treatment such as radiation therapy or in patients who have previously had CNS treatment as chemotherapy intrathecally.

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

Cases of cardiomyopathy with subsequent death have been reported following experimental high dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation.

Safety in infants has not been established.
This medicinal product contains 2.14mg of sodium per 1ml dose. To be taken into consideration by patients on a controlled sodium diet

4.5 Interaction with other medicinal products and other forms of interaction

Cardiac Glycosides:
The gastro-intestinal absorption of oral digoxin tablets may be substantially reduced if digoxin is combined with chemotherapeutics (including cytarabine). This is probably dependent on temporary damage to the mucosa. The plasma levels of digoxin must therefore be monitored. 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.

Limited data suggest that the extent of gastro-intestinal absorption of digitoxin is not substantially affected by concomitant administration of combination chemotherapy regimens known to decrease absorption of digoxin.

Therefore, monitoring of plasma digoxin levels may be indicated in patients receiving similar combination chemotherapy regimens. The utilization of digitoxin for such patients may be considered as an alternative.

Combining Cytarabine with other oncolytic agents, myelosuppressive drugs or radiation treatment can sometimes reduce the immunosuppressive effect of these drugs. Modification of the dosage may be necessary. Cytarabine is often administered in combination with other drugs.

Anti-Infective Agents:
An in vitro study has shown that cytarabine can counteract the effect of gentamicin against Klebsiella pneumoniae. Limited data may suggest that cytarabine may antagonise the anti-infective activity of, fluorocytosine possibly by competitive inhibition of the anti-infective uptake by fungi.

The concomitant administration of cytarabine with other cytotoxic drugs can potentiate toxicity, especially bone marrow toxicity.

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. Limited data may suggest that cytarabine may antagonise the anti-infective activity of flucytosine, possibly by competitive inhibition of the anti-infective uptake by fungi.

Immunosuppressive agents:
Due to the immunosuppressive action of cytarabine, 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.

Increased toxicity may occur following the concurrent use of cytarabine and idarubicin.

4.6 Fertility, pregnancy and lactation

Pregnancy
During pregnancy, cytarabine may only be administered on strict indication, in which context the benefits of the drug for the mother must be weighed against the possible dangers to the foetus. Animal studies have shown that cytarabine has embryotoxic and teratogenic effects (see section 5.3).

Men and women must use effective contraceptives during treatment and for six months thereafter.

Breastfeeding
It is not known whether cytarabine is secreted in mother's milk. As many drugs are secreted in mother's milk and as cytarabine can be responsible for serious side effects in the neonate, breastfeeding should be stopped during treatment with Cytarabine.

Fertility
Fertility studies to assess the reproductive toxicity of cytarabine have not been conducted. Gonadal suppression, resulting in amenorrhea or azoospermia, may occur in patients taking cytarabine therapy, especially in combination with alkylating agents. In general, these effects appear to be related to dose and length of therapy and may be irreversible, Given that cytarabine has a mutagenic potential which could induce chromosomal damage in the human spermatozoa, males undergoing cytarabine treatment and their partner should be advised to use reliable contraceptive method.

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 a reduced ability to drive or operate machinery, and should be warned of the risk and advised to avoid this type of activity if this occurs.

Patients who are subject to incidental occurrences of vomiting, dizziness and eye complaints are advised not to drive vehicles or operate machinery.

4.8 Undesirable effects

Side effects of cytarabine are dose dependent. The most common are gastrointestinal side effects, and cytarabine is toxic to the bone marrow (myelosuppression) and causes haematological side effects.
Evaluation of undesirable effects is based on the following frequency information: 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 (frequency cannot be estimated from available data).

Cytarabine Syndrome (immunoallergic effect): this is characterised by fever, myalgia, bone pain, occasionally chest pain, exanthema, maculopapular rash, conjunctivitis, nausea and malaise. It usually occurs 6-12 hours after 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. If treatment is effective, therapy with cytarabine may be continued.

Blood and lymphatic system disorders
Very common (> 1/10):
myelosuppression, neutropenia, reticulocytopenia

Common (≥1/100 to <1/10):
Anaemia, megaloblastosis, leukopenia, granulocytopenia, thrombocytopenia, bleeding,
The above appear to be more evident after high doses and continuous infusions; the severity depends on the dose of the drug and schedule of administration.

Infections and Infestations
Uncommon (≥1/1,000 to <1/100):
Pneumonia, sepsis, immunosuppression.

Metabolism and nutrition disorders
Common (≥1/100 to <1/10)*:*
Anorexia, hyperuricaemia secondary to lysis of neoplastic cells

Immune system disorders
Very common (≥ 1/10)*:*
Cytarabine (Ara-C) syndrome: fever, myalgia, bone pain, incidental chest pain, exanthema, conjunctivitis and nausea may occur 6-12 hours after the start of the therapy. Corticosteroids can be used as prophylaxis and therapy. If these are effective, the therapy with cytarabine can be continued. Myelosuppression can be severe and prolonged.

Uncommon (≥1/1,000 to <1/100):
Allergic oedema, anaphylaxis. One case of anaphylaxis has been reported, which resulted in cardiopulmonary arrest for which resuscitation had to be applied. This occurred immediately after intravenous administration of cytarabine.

Very rare (<1/10,000)
Anaphylaxis.
One case of anaphylaxis that resulted in cardiopulmonary arrest and necessitated resuscitation has been reported

Nervous system disorders
The chance of CNS toxicity increases if cytarabine is administered intrathecally, the intrathecally cytarabine treatment is combined with other treatments which are toxic to the CNS, such as radiation, high dose therapy, or intrathecal methotrexate, or if the cytarabine treatment is intrathecally administered with short intervals or in doses above 30 mg/m².

Common (≥1/100 to <1/10)*):*
In the event of high dosages, cerebellar or cerebral toxicity with decreased of consciousness level, dysarthria, nystagmus, seizure (when given intrathecally), headache, dizziness, neuritis or neural toxicity and pain.

Uncommon (≥1/1,000 to <1/100)*:*
Peripheral neuropathy and paraplegia in the case of intrathecal administration.
Headache

Very rare (<1/10,000)*:*
Severe spinal cord toxicity (even leading to necrotising leukoencephalopathy, paraplegia or quadriplegia paralysis and blindness) has been reported after intrathecal treatment.
Severe spinal cord toxicity is predominantly associated with intrathecal administration, but isolated cases have also been reported with high intravenous doses during combination chemotherapeutic regimens. Other isolated neurotoxicities have been reported.

Eye disorders
Very common (> 1/10):
Conjunctivitis (high dose therapy)

Common (≥1/100 to <1/10)*:*
Reversible haemorrhagic conjunctivitis (photophobia, stinging, visual disorders, increased lacrymation), keratitis.
Locally administered glucocorticoids are recommended as prophylaxis against haemorrhagic conjunctivitis.

Very rare (<1/10,000):
Blindness has been reported after intrathecal treatment.

Cardiac disorders
Uncommon (≥1/1,000 to <1/100):
Pericarditis, chest pain.

Very rare(<1/10,000)*:*
Arrhythmia. Cardiomyopathy has been reported after cytarabine therapy.

Respiratory, thoracic and mediastinal disorders
Uncommon (<1/10,000)*:*
Pneumonia, dyspnea, sore throat, interstitial pneumonitis, syndrome of sudden respiratory distress progressing to pulmonary oedema.

Gastrointestinal disorders *Common* (≥1/100 to <1/10):
Mucositis, stomatitis, anorexia, dysphagia, abdominal pain, nausea, vomiting, diarrhoea, oral/anal inflammation or ulceration.

Uncommon (≥1/1,000 to <1/100):
Oesophagitis, oesophageal ulceration, pneumatosis, cystoides intestinalis, necrotising colitis, GI perforation, nausea, peritonitis, vomiting after intrathecal administration

Very rare (<1/10,000):
Pancreatitis, when intravenous doses are given quickly, patients may become nauseated and may vomit for several hours afterwards. The problem tends to be less severe when cytarabine is infused.

Hepato-biliary disorders
Common (≥1/100 to <1/10):
Reversible effects on the liver with increased enzyme values, jaundice.

Skin and subcutaneous tissue disorders
Common (≥1/100 to <1/10):
Reversible side effects to the skin, such as erythema, bullosis, urticaria, vasculitis, alopecia, painful redness and blistering on the palms of the hands and soles of the feet (high dose therapy), lentigo, cellulitis at the injection site, skin ulceration, pruritis, burning pain on the palms of the hands and soles of the feet.
Freckling has also been reported.

Very rare (<1/10,000)*:*
Neutrophilic eccrine hidradenitis.

Musculoskeletal, connective tissue and bone disorders
Uncommon (≥1/1,000 to <1/100):
Myalgia, arthralgia, joint pain.

Very rare (<1/10,000)*:*
Rhabdomyolysis has been reported after cytarabine therapy.

Renal and urinary passage disorders
Common (≥1/100 to <1/10):
Kidney function disorders, urinary retention.

General disorders and administration site disorders
Common (≥1/100 to <1/10):
Fever, thrombophlebitis at the injection site, hyperuricaemia.

Uncommon (≥1/1,000 to <1/100):
Fever after intrathecal administration.

Adverse effects due to high dose cytarabine treatment, other than those seen with conventional doses include:
Severe and at times fatal CNS, gastro-intestinal and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) have been reported following experimental cytarabine dosage schedules. These reactions include reversible corneal toxicity, cerebral and cerebellar dysfunction, usually reversible, severe gastrointestinal ulceration, including pneumatosis cysteroides intestinalis, leading to peritonitis; sepsis and liver abscess; and pulmonary oedema.

Blood and lympthatic system disorders
Seen as profound pancytopenia which may last 15-25 days along with more severe bone marrow aplasia than that observed at conventional doses.

Nervous system disorders
After treatment with high doses of cytarabine, symptoms of cerebral or cerebellar influences 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. readiotherapy) 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. – is combined with another CNS toxic treatment such as radiation therapy or high dose of a cytotoxic agent.

Eye disorders
Reversible corneal lesion and haemorrhagic conjunctivitis have been described. These phenomena can be prevented or decreased by installation of corticosteroid eye drops.

Respiratory, thoracic and mediastinal disorders
Clinical signs as present in pulmonary oedema/ARDS may develop, particularly in high=-dose therapy. The reaction is probably caused by an alveolar capillary injury. It is difficult to make an assessment of frequencies (stated as 10-26% in different publications) since the patients usually have been in relapse where other factors may contribute to this reaction.

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. Pancreatitis has also been observed after high-dose therapy.

Hepatobiliary disorders
Liver abscesses, hepatomegaly and Budd-Chiari-syndrome (hepatic venous thrombosis) have been observed after high dose therapy.

Others
Following cytarabine therapy, cardiomyopathy and rhabdomyolysis have been reported. The gastrointestinal undesirable effects are reduced if cytarabine is administered as infusion. Local glucocorticoids are recommended as prophylaxis of hemorrhagic conjunctivitis.

Amenorrhoea and azoospermia.

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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

There is no specific antidote for cytarabine overdose. In the event of an overdose, therapy must be stopped, followed by treatment of the subsequent bone marrow depression, including total blood or platelet transfusion and antibiotics, as required.

Twelve doses of 4.5 g/m2 by IV infusion over one hour every 12 hours induces irreversible and fatal central nervous system toxicity

Cytarabine can be removed by means of haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: Antimetabolite (pyrimidine analogue)

ATC Code: L01BC01

Cytarabine contains the active ingredient cytarabine, an antimetabolite from the series of pyrimidine antagonists.

Pharmacodynamic effects
Cytarabine is a cell-cycle-phase-specific antineoplastic agent, which can only affect cells during the S-phase of cell division. It is converted intracellularly into cytarabine-5’ triphosphate (ara-CTP), which is the active metabolite.

Mechanism of action
The mechanism of action is not completely understood, but it appears that ara-CTP acts primarily through inhibition of DNA polymerase. Incorporation into DNA and RNA may also contribute to cytarabine cytotoxicity.

Clinical efficacy and safety
Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture.
Cytarabine has no effect on non-proliferating cells nor on proliferating cells unless in the S phase. It is a cell cycle specific antineoplastic drug.

After 24 hours, 80% of a dose has been eliminated either as the inactive metabolite or as the unchanged cytarabine, mostly in urine but some in bile.

CSF levels of 50% of plasma levels are achieved with IV infusion.

Cytarabine is rapidly and widely distributed into tissues, crosses the blood brain barrier and also the placenta.

5.2 Pharmacokinetic properties

Absorption
Cytarabine is rapidly metabolised and is orally ineffective. Less than 20% of a dose administered orally is absorbed in the gastrointestinal tract.

In the event of continuous intravenous administration, virtually constant plasma levels are achieved.

After subcutaneous or intramuscular administration of cytarabine, peak plasma levels are achieved approximately 20 to 60 minutes after injection which are significantly lower than after intravenous administration.

Cytarabine serum levels can vary considerably from patient to patient for an identical dose. Some studies have shown that these variations could be linked to the clinical response: high serum levels guarantee the best chance of haematological remissions.

Distribution
Cytarabine has a distribution volume of 0.7 l/kg.

Biotransformation Cytarabine is converted rapidly by deoxycitidine kinase and other nucleotidases into its active form (cytarabine-5' triphosphate) by phosphorylation in leukaemic blast cells and in healthy bone marrow. Metabolism into the inactive compound uracilarabinoside (1−beta−D−arabinofuranosyluracil) by means of cytidine deaminase activity takes place primarily in the liver, and to a lesser extent in the other tissues and blood.

It is assumed that the balance between kinase and deaminase levels can form an important factor in the determination of whether the cell is sensitive or resistant to cytarabine.

Protein binding
Binding to plasma protein is low (13.3%) with concentrations of 0.005-1 mg/l.

The percentage of bound drug was independent of the concentration within the limits indicated.

Elimination After a rapid intravenous infusion of cytarabine, biphasic elimination from the blood takes place. There is an initial distribution phase with a half life of approx. 10 minutes, followed by a secondary elimination phase with a half life of 1-3 hours.

After 24 hours, approx. 80% of the administered cytarabine is found in the urine, 90% of which is excreted as inactivated metabolite and 10% as unchanged cytarabine.

Due to the low cytarabine deaminase activity in the cerebrospinal fluid, cytarabine has an elimination half life in the CNS of 3-3.5 hours.

5.3 Preclinical safety data

Studies have reported that cytarabine is genotoxic (in vivo and in vitro) as well as embryotoxic and teratogenic, if exposed to pregnant mammals during the organogenesis in clinically relevant dosage regimen.

It is also reported that cytarabine causes damage to the developing brain if administered to newborn mammals (period equivalent to third trimester in humans) and increases the frequency of abnormal spermatozoa in vivo in mice.

It has been shown that cytarabine is carcinogenic in animals. The possibility of a comparable effect must be taken into account when determining the long-term strategy for the patient.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium lactate
Lactic acid
Water for injections

6.2 Incompatibilities

Cytarabine is physically incompatible with various drugs, i.e., heparin, insulin regular, methotrexate, 5-fluorouracil, carbenicillin sodium, cephalothin sodium, gentamicin sulphate, nafcillin, oxacillin, hydrocortisone sodium succinate, penicillin G sodium, benzylpenicillin and methylprednisolone sodium succinate.

However the incompatibility depends on several factors (e.g. concentrations for 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 except those mentioned in section 6.6

6.3 Shelf life

Unopened: 2 years

The product should be used immediately after opening

Storage life after reconstitution
Chemical and physical stability after dilution with 0.9 % sodium chloride solution and 5 % glucose solution has been demonstrated for 4 days at 2-8^{o}C and for 24 hours when stored at a temperature below 25^{o}C.

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

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in original packaging.

Do not refrigerate or freeze

6.5 Nature and contents of container

Clear glass vials type 1 with butyl rubber closure

Vial sizes: 10 ml, 20ml, 40ml

1 vial per carton
Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The diluted solution for infusion is a clear, colourless or pale yellow solution.

Cytarabine must be diluted for infusion with 0.9 % sodium chloride solution or 5% glucose solution.

Compatibility with 0.9 % sodium chloride solution and 5 % glucose solution has been studied in concentrations of 0.2 – 3.2mg/ml in PVC infusion bags, PE infusion vials and perfusion syringes.

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 always 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 balnd 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. Spilled or leaked product can be inactivated with 5% sodium hypochlorite solution. 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.

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

7 MARKETING AUTHORISATION HOLDER

Fannin Limited
Fannin House
South County Business Park
Leopardstown
Dublin 18

8 MARKETING AUTHORISATION NUMBER

PA1457/007/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 10th November 2006

Date of Last Renewal: 10th November 2011

10 DATE OF REVISION OF THE TEXT

May 2016