SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cytarabine 20 mg/ml Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml solution contains 20 mg of Cytarabine.

Each vial of 2 ml of solution contains 40 mg of Cytarabine.

Each vial of 5 ml of solution contains 100 mg of Cytarabine.

Excipient with known effect:

Each vial contains <1 mmol sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear, colourless solution, free from visible particles.

pH: 7.0 to 9.5

Osmolarity: Approx. 300 mOsmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the induction of remission in acute myeloid leukaemia in adults and for other acute leukaemias of adults and children including prophylaxis and treatment of CNS involvement (meningeal leukaemia).

4.2 Posology and method of administration

Cytarabine 20 mg/ml solution for injection/infusion is intended for intravenous, intramuscular, subcutaneous or intrathecal use.

Subcutaneous injection is generally well tolerated, and may be recommended when used in maintenance therapy.

Cytarabine 20 mg/ml solution for injection/infusion can be diluted with Sterilised Water for Injections, Glucose Intravenous Infusion or Sodium Chloride Intravenous Infusion.

Treatment with cytarabine should be initiated by, or be in consultation with, a doctor with extensive experience in treatment with cytostatics. Only general recommendations can be given, as acute leukaemia is almost exclusively treated with combinations of cytostatics.
Dosage recommendations, may be made according to body weight (mg/kg) or according to
BSA(mg/m^2). Dose recommendation may be converted from those in terms of bodyweight to those related to surface area by means of nomograms.

Remission Induction:
Continuous treatment: The usual dose in leukaemia is 2 mg/kg/day 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 4 mg/kg/day until a therapeutic response or toxicity is evident. Almost all patients can be carried to toxicity with these doses.

Alternatively, 0.5 to 1 mg/kg/day 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 from one hour infusions have been satisfactory in the majority of patients.

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

Evidence of bone 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 remission nor toxicity after a trial period, the cautious administration of higher doses is warranted. Generally patients tolerate higher doses given by rapid intravenous injection rather than slow infusion. This difference is due to the rapid metabolism of Cytarabine and the consequent short duration of action of the high dose.

Cytarabine has been given in doses of 100-200 mg/m^2/24 hours by continuous infusion for 5-7 days alone or combination with other cytostatics including for instance an anthracycline has been used. Additional cycles may be administered at intervals of 2-4 weeks, until remission is achieved or unacceptable toxicity occurs.

Maintenance therapy: To maintain remission, doses of 1 mg/kg may be given intravenously or subcutaneously, once or twice weekly.

Cytarabine has also been administered in doses of 100-200 mg/m^2, as continuous infusion for 5 days at monthly intervals as monotherapy or in combination with other cytostatics.

Intrathecally
Doses between 5 and 30 mg/m² BSA have been administered.
For the treatment of meningeal leukaemia, usually a dose of 30 mg/m² BSA is given once every 4 days until cerebrospinal fluid findings are normal, followed by one additional dose. The injection should be slow. See section 4.8.

High dosage:
Cytarabine, under strict medical surveillance, is administered as monotherapy or in combination with other cytostatics, **2-3 g/m²**, as intravenous infusion, for 1-3 hours every 12 hours for 2-6 days (total of 12 doses per cycle). A total treatment dose of **36 g/m²** should not be exceeded. Frequency of treatment cycles depends on the response to treatment and haematological and non-haematogological toxicity. Also refer to precautions (4.4) for treatment stopping requirements.

Paediatric patients: Children appear to tolerate higher doses than adults and, where dose ranges are quoted, the children should receive the higher dose and the adults the lower.

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

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

Elderly patients:
High dose therapy in patients > 60 years should be administered only after careful risk benefit-evaluation. 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 leucopenia, thrombocytopenia, and anaemia, with appropriate initiation of supportive therapy when indicated.

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

4.3 Contraindications

Hypersensitivity to cytarabine or to any of the excipients listed in section 6.1.

Anaemia, leucopenia and thrombocytopenia of non-malignant aetiology (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.

During pregnancy, cytarabine should only be administrated 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

General:

Only physicians experienced in cancer chemotherapy should use cytarabine.

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

Facilities should be available for management of complications, possibly fatal bone marrow suppression (infection resulting from granulocytopenia and other impaired body defences, and haemorrhage secondary to thrombocytopenia).

Patients receiving cytarabine must be monitored closely. Frequent platelet and leucocyte counts are mandatory. Therapy should be suspended or modified when drug-induced marrow depression has resulted in a platelet count under 50,000 or a polymorphonuclear 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, therapy may be restarted 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.

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.

Anaphylactic reactions have occurred with cytarabine treatment. Anaphylaxis that resulted in acute cardiopulmonary arrest and necessitated resuscitation has been reported. This occurred immediately after intravenous cytarabine was administered.

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

The human liver apparently detoxifies a substantial fraction of an administered dose of cytarabine. In particular, patients with renal or hepatic impairment may have a higher likelihood of CNS toxicity after high-dose treatment with cytarabine. The drug should be used with caution and at reduced dose in patients whose liver function is poor. However, dosage reduction does not appear to be necessary in patients with impaired renal function.
Concurrent granulocyte-transfusion should be avoided as severe respiratory insufficiency have been reported.

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.

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.

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.

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.

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

Peripheral motor and sensory neuropathies after consolidation with high doses of cytarabine, daunorubicin, and asparaginase have occurred in adult patients with acute non lymphocytic leukaemia.

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 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.

Paediatric population
Safety in infants is not established.

Sodium

This medicine contains less than 1mmol sodium (23 mg) per 5 ml, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

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. Limited data suggest that the extent of GI 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.

Gentamicin
An in vitro study indicates that cytarabine may antagonise the activity of gentamicin against *Klebsiella pneumoniae*. 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.

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.

Use of cytarabine alone or in combination with other immunosuppressive agents
Due to the immunosuppresive 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.

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

Methotrexate:
There is evidence of pharmacodynamic interaction between methotrexate and cytarabine leading to encephalopathy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Women have to use effective contraception during and for at least 6 months after treatment. 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 effective contraception during and for at least 3 months after treatment.

Pregnancy

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

Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, a patient who is or who may become pregnant while on cytarabine should be apprised of the potential risk to the foetus and the advisability of pregnancy continuation. There is a definite, but considerably reduced risk if therapy is initiated during the second or third trimester. Although normal infants have been delivered to patients treated in all three trimesters of pregnancy, follow-up of such infants would be advisable.

Breast-feeding
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cytarabine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
This product should not normally be administered to mothers who are breastfeeding.

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 (see section 4.8).

4.7 Effects on ability to drive and use machines

Cytarabine has no influence on the ability to drive and use machines.

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

The following adverse events have been reported in association with cytarabine therapy. 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).

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	*Uncommon:* Sepsis (immunosuppression), cellulitis at

	injection site *Not known:* Pneumonia, liver abscess
Immune system disorders	*Not known:* Anaphylaxis, allergic oedema
Neoplasms benign malignant and unspecified (including cysts and polyps)	*Uncommon:* Lentigo
Blood and lymphatic system disorders	*Common:* Thrombocytopenia, anaemia, megaloblastosis, leucopenia *Not known:* Neutropenia, febrile neutropenia
Metabolism and nutrition disorders	*Common:* Anorexia, hyperuricaemia
Nervous system disorders	*Common:* At high doses cerebellar or cerebral influence with deterioration of the level of consciousness, dysarthria, nystagmus *Uncommon:* Headache, peripheral neuropathy and paraplegia at intrathecal administration *Not known:* Dizziness, neuritis, neural toxicity
Eye disorders	*Common:* Reversible haemorrhagic conjunctivitis (photophobia, burning, visual disturbance, increased lacrimation), keratitis, conjunctivitis (may occur with rash)
Cardiac disorders	*Uncommon:* Pericarditis *Very rare:* Arrythmia *Not known:* Sinus bradycardia
Vascular disorders	*Not known:* Thrombophlebitis
Respiratory, thoracic and mediastinal disorders	*Uncommon:* Dyspnoea, sore throat
Gastrointestinal disorders	*Common:* Dysphagia, nausea, vomiting, diarrhoea, oral and anal inflammation or ulceration, abdominal pain, *Uncommon:* Oesophagitis, oesophageal ulceration, pneumatosis cystoides intestinalis, necrotising colitis, peritonitis

	Not known: Pancreatitis, gastrointestinal necrosis
Hepatobiliary disorders	*Common:* Reversible effects on the liver with increased enzyme levels *Not known:* Hepatic dysfunction, jaundice
Skin and subcutaneous tissue disorders	*Common:* Reversible undesirable effects to the skin, such as erythema, bullous dermatitis, urticaria, vasculitis, alopecia (high dose therapy) *Uncommon:* Skin ulceration, pruritus *Very rare:* Neutrophilic eccrine hidradenitis *Not known:* Freckling, rash, Palmar-plantar erythrodysaesthesia syndrome
Musculoskeletal and connective tissue disorders	*Uncommon:* Myalgia, arthralgia
Renal and urinary disorders	*Common:* Renal impairment, urinary retention
General disorders and administration site conditions	*Common:* Fever, thrombophlebitis at the site of injection. *Not known:* Chest pain and injection site reaction (pain and inflammation at the subcutaneous injection sites)
Investigations	*Not known:* Reduced reticulocytes, cellular changes in the morphology of bone marrow and peripheral smears

Cytarabine (Ara-C) Syndrome (Immunoallergic effect):
Fever, myalgia, bone pain, occasional chest pain, exanthema, conjuctivitis and nausea may occur 6-12 h after start of therapy. Corticosteroids may be considered as prophylaxis and therapy. If they are effective, therapy with cytarabine may be continued.

After Intrathecal use
Nervous system disorders
The risk of CNS toxicity increases if the cytarabine treatment - given as high dose i.v. or intrathecally - is combined with another CNS toxic treatment such as radiation therapy, high dose or intrathecal methotrexate or when given intrathecally in short intervals or in doses above 30 mg/m².

After intrathecal treatment necrotising leukencephalopathy, bone marrow depression, myelopathy resulting in para-or quadriplegia, paralysis and other isolated neurotoxicities have been reported.

Eye disorders
Blindness.

Gastrointestinal disorders
Nausea, vomiting.

General disorders and administration site conditions
Headache, fever and/or other symptoms of an arachnoiditis.

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; somnolence; convulsion; severe gastrointestinal ulceration, including pneumatosis cysteroides intestinalis , leading to peritonitis ; sepsis and liver abscess; and pulmonary oedema.
Infections and infestations:
Sepsis, liver abscess

Blood and lymphatic 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 influence like personality changes, affected alertness, dysarthria, ataxia, tremor, nystagmus, headache, confusion, somnolence, dizziness, coma, convulsions, peripheral motor and sensory neuropathies 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.- is combined with another CNS toxic treatment such as radiation therapy or high dose of a cytotoxic agent

***Corneal and conjunctival toxicity*:**
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.

A diffuse interstitial pneumonitis without clear cause that may have been related to cytarabine was reported in patients treated with experimental intermediate doses of

cytarabine (1g/m^2) with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, VP-16).

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary oedema and a radiographically pronounced cardiomegaly has been reported following experimental high dose therapy with cytarabine used for the treatment of relapsed leukemia; fatal outcome has been reported.

Gastrointestinal disorders:
Gastrointestinal necrosis, necrotising colitis, gastrointestinal ulceration (including pneumatosis cystoides intestinalis leading to peritonitis).
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.

Hepatobiliary disorders:
Liver damage with increased hyperbilirubinemia hepatomegaly, Budd-Chiari-syndrome (hepatic venous thrombosis) and pancreatitis have been observed after high-dose therapy.

Skin and subcutaneous tissue disorders:
Skin rash leading to desquamation, alopecia.

Others:
Following cytarabine therapy, cardiomyopathy with subsequent death and rhabdomyolysis have been reported. One case of anaphylaxis that resulted in cardiopulmonary arrest and necessitated resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine.

The gastrointestinal undesirable effects are reduced if cytarabine is administered as infusion. Local glucocorticoids are recommended as prophylaxis of haemorrhagic conjunctivitis.

Amenorrhoea and azoospermia (see section 4.6)

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.

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 the national reporting system Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no specific antidote for cytarabine overdose. Cessation of therapy followed by management of ensuing bone marrow depression including whole blood or platelet transfusion and antibiotics as required.

Twelve doses of 4.5 g/m^2 by IV infusion over one hour every 12 hours induces irreversible and fatal central nervous system toxicity.

In case of intrathecal overdose: liquor should be replaced by isotonic saline solution immediately.

Cytarabine may be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, antimetabolites, pyrimidine analogue
ATC code: L01BC01

Mechanism of action
Cytarabine, a pyrimidine nucleoside analogue, is an antineoplastic agent which inhibits the synthesis of deoxyribonucleic acid specifically in the S phase of the cell cycle. 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 via its active triposhphate metabolite arabinofuranosyl cytosine triphosphate ARA-CTP, although inhibition of cytidylic kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytocidal actions.

High dose cytarabine regimes can overcome the resistance of leukaemic cells no longer responding to conventional doses. Several mechanism appear to be involved to this resistance:
Increases in the quantity of substrate
Increase in the intracellular pool of ARA-CTP, since there is a positive correlation between intracellular retention of ARA-CTP and percentage of cells in S-phase.

5.2 Pharmacokinetic properties

Intravenous administration

Biotransformation

Cytarabine is deaminated to arabinofuranosyl uracil in the liver and kidneys. Cytarabine appears to be metabolised rapidly, primarily by the liver and perhaps by the kidney.

Elimination

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 inactive deaminated product ,arabinofuranosyl uracil (ARA-U). 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. 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.

Subcutaneous administration

Absorption

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.

Intrathecal administration

Absorption

Cytarabine should be administered intrathecally as prophylaxis and when treating CNS leukaemia, as cytarabine administered by the intravenous route crosses the blood-brain barrier to a limited extent only. Intrathecal administration of cytarabine results in very low plasma levels.

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

Sodium Chloride

Sodium hydroxide (for pH adjustment)

Hydrochloric acid concentrate (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, insulin-regular, 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 product except those mentioned in section 6.6.

6.3 Shelf life

Before use: 3 years.

In-use: Chemical and physical in-use stability has demonstrated at 0.04 mg/ml, 0.1 mg/ml, 1.0 mg/ml and 4.0 mg/ml concentration. The product is stable for 8 days at below 25°C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 ml: Clear glass vial with a butyl rubber stopper and aluminium flip off blue seal.
5 ml: Clear glass vial with a butyl rubber stopper and aluminium flip off red seal.

Glass vial is wrapped with superficial plastic sheathing along with Non-PVC base.

Pack sizes:
2 ml: 1 vial, 5 vials and 25 vials
5 ml: 1 vial, 5 vials and 25 vials

Not all presentations and pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only. Any unused solution should be discarded.

Cytarabine 20 mg/ml solution for injection/infusion is intended for intravenous, intramuscular, subcutaneous or intrathecal use.

The diluted solution should be clear, colourless and 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 20 mg/ml solution for Injection/Infusion can be diluted with Sterilised Water for Injection, 5% Dextrose injection or 0.9% Sodium Chloride injection.

If Cytarabine comes in contact with skin, the exposed area should be rinsed with large amounts of water and then thoroughly washed with soap and water. If the solution gets into the eyes, rinse very carefully with large amounts of water, whereupon an eye specialist should be consulted immediately.

Pregnant staff should be excluded from working with this drug.

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

To destroy, place in high risk (for cytotoxic) waste disposal bag and incinerate at 1100°C. If spills occur, restrict access to the affected area and adequate protection including 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 pill area should be cleaned with copious amounts of water. Place the contaminated material in a leak proof disposal bag for cytotoxic and incinerate at 1100°C.

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited,

Sage House, 319 Pinner Road,

North Harrow, Middlesex, HA1 4HF,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0538

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/08/2023

10 DATE OF REVISION OF THE TEXT

30/12/2024