

**Public Assessment Report**  
**Decentralised Procedure**

**Cytarabine 100mg/ml Solution for Injection or Infusion**

**UK/H/1641/001/DC**  
**UK licence no: PL 20075/0121**

**Accord Healthcare Limited**

## LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Accord Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Cytarabine 100mg/ml Solution for Injection or Infusion (PL 20075/0121). This prescription-only medicine (POM) is used in the in the treatment of acute myeloid leukaemia in adults and for other acute leukaemias.

Cytarabine Injection/ Injection contain the active ingredient cytarabine. Cytarabine is one of a group of medicines known as cytotoxics; these medicines are used in the treatment of acute leukaemias (cancer of blood where you have too many white blood cells). Cytarabine interferes with the growth of cancer cell, which are eventually destroyed.

The test product was considered to be the same as the reference product Cytarabine 100mg/ml Injection (PL 00032/0198), first licensed in the UK in June 1999 to Pharmacia Limited.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Cytarabine 100mg/mlSolution for Injection or Infusion outweigh the risks; hence a Marketing Authorisation has been granted.

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## Module 1

<b>Product Name</b>	Cytarabine 100mg/ml solution for injection or infusion
<b>Type of Application</b>	Generic, Article 10.1
<b>Active Substance</b>	Cytarabine
<b>Form</b>	Solution For Injection or infusion
<b>Strength</b>	100mg/ml
<b>MA Holder</b>	Accord Healthcare Limited, Sage House, 319 Pinner Road, Harrow, Middlesex HA1 4HF UK
<b>RMS</b>	UK
<b>CMS</b>	Bulgaria, Estonia, Latvia and Lithuania.
<b>Procedure Number</b>	UK/H/1641/001/DC
<b>End of Procedure</b>	16 <sup>th</sup> November 2009

## Module 2

### SUMMARY OF PRODUCT CHARACTERISTICS

#### 1 NAME OF THE MEDICINAL PRODUCT

Cytarabine 100 mg/ml Solution for Injection or Infusion

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 100 mg Cytarabine.

Each 1 ml vial contains 100 mg of Cytarabine.

Each 5 ml vial contains 500 mg of Cytarabine.

Each 10 ml vial contains 1000 mg of Cytarabine.

For full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Solution for injection or infusion.

The product is a clear, colourless solution, which is practically free from particles.

#### 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.

**Cytarabine should not be administered by the intrathecal route.**

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

##### 1. Remission induction:

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:

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.

***Children:***

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.

***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 leucopenia, thrombocytopenia, and anaemia, with appropriate initiation of supportive therapy when indicated.

**4.3 Contraindications**

Hypersensitivity to the Cytarabine or to any of the excipients of cytarabine injection.

Therapy with Cytarabine should not be considered in patients with pre-existing drug-induced bone marrow suppression, unless the clinician feels that such management offers the most hopeful alternative for the patient. Cytarabine should not be used in the management of non-malignant disease, except for immunosuppression.

**4.4 Special warnings and precautions for use****Warnings:**

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

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. One case of anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of Cytarabine.

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 Cytarabine dose schedules. 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.

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

**Precautions:**

Patients receiving Cytarabine must be monitored closely. Frequent platelet and leucocyte counts are mandatory. Suspend or modify therapy when drug induced marrow depression has resulted in a platelet count under 50,000 or a polymorphonuclear 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 five to seven 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 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.

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.

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.

The human liver apparently detoxifies a substantial fraction of an administered dose. 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.

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

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.

**Immunosuppressant Effects/Increased Susceptibility to Infections.**

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cytarabine, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving cytarabine. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

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

Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyldigoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without Cytarabine or procarbazine. Steady-state plasma digitoxin concentrations did not appear to change. Therefore, monitoring of plasma digoxin levels may be indicated in patients receiving similar combination chemotherapy regimens. The utilisation of digitoxin for such patients may be considered as an alternative.

An in-vitro interaction study between gentamicin and Cytarabine showed a Cytarabine related antagonism for the susceptibility of *K. pneumoniae* strains. In patients on Cytarabine being treated with gentamicin for a *K.pneumoniae* infection, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

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

##### **Lactation**

This product should not normally be administered to patients who are pregnant or to mothers who are breastfeeding.

**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 ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data)

Undesirable effects from cytarabine are dose-dependent. Most common are gastro-intestinal undesirable effects. Cytarabine is toxic to the bone marrow, and causes haematological undesirable effects.

***Cardiac disorders:***

Uncommon: Pericarditis

Very rare: Arrhythmia.

***Blood and lymphatic system disorders:***

Common: Anaemia, megaloblastosis, leucopenia, thrombocytopenia.

***Nervous system disorders:***

Common: At high doses cerebellar or cerebral influence with deterioration of the level of consciousness, dysarthria, nystagmus.

Uncommon: headache.

***Eye disorders:***

Common: Reversible haemorrhagic conjunctivitis (photophobia, burning, visual disturbance, increased lacrimation), keratitis.

***Respiratory, thoracic and mediastinal disorders:***

Uncommon: Pneumonia, dyspnea, sore throat.

***Gastrointestinal disorders:***

Common: Dysphagia, abdominal pain, nausea, vomiting, diarrhoea, oral / anal inflammation or ulceration.

Uncommon: Esophagitis, esophageal ulceration, pneumatosis cystoides intestinalis, necrotising colitis.

***Renal and urinary disorders:***

Uncommon: Renal impairment, urinary retention

***Skin and subcutaneous tissue disorders:***

Common: Reversible undesirable effects to the skin, such as erythema, bullous dermatitis, urticaria, vasculitis, alopecia.

Uncommon: Skin ulceration, pruritus, burning pain of palms and soles.

Very rare: Neutrophilic eccrine hidradenitis.

***Musculoskeletal and connective tissue disorders:***

Uncommon: Myalgia, arthralgia.

***Metabolism and nutrition disorders:***

Common: Anorexia, hyperuricaemia.

***Infections and infestations:***

Uncommon: Sepsis (immunosuppression), cellulitis at injection site.

***Neoplasm benign, malignant and unspecified (Incl. cysts and polyps)***

Uncommon: Lentigo.

***General disorders and administration site conditions***

Common: Fever, thrombophlebitis at the injection site.

Uncommon: Chest pain.

***Immune system disorders***

Uncommon: Anaphylaxis.

***Hepatobiliary disorders***

Common: Reversible effects on the liver with increased enzyme levels.

Uncommon: Jaundice.

***Cytarabine (Ara-C) Syndrome:***

Fever, myalgia, bone pain, occasional chest pain, exanthema, conjunctivitis 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.

***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 (see table). 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.

***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.

***Others:***

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

The gastro-intestinal undesirable effects are reduced if cytarabine is administered as infusion. Local glucocorticoides are recommended as prophylaxis of haemorrhagic conjunctivitis.

**4.9 Overdose**

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

Cytarabine may be removed by haemodialysis.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: 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 cytotoxic 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 in demonstrable circulating drug as early as 5 minutes after injection.

### **5.3 Preclinical safety data**

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Macrogol 400  
Trometamol  
Water for Injections

### **6.2 Incompatibilities**

Incompatibilities with: Heparin, insulin, Methotrexate, 5-fluorouracil, nafcillin, oxacillin, penicillin G, methyl-prednisolone succinate.

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

### **6.3 Shelf life**

2 years

In use stability: Chemical and physical in-use stability has been demonstrated in sodium chloride injection (0.9 % w/v) and dextrose injection (5% w/v) for up to 24 hours at temperature below 25° C and for up to 72 hours at 2-8°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° C, unless dilution has taken place in controlled and validated aseptic conditions.

### **6.4 Special precautions for storage**

Do not store above 25° C.  
Keep the vial in the outer carton in order to protect from light.  
Do not refrigerate.

### **6.5 Nature and contents of container**

For 1 ml,  
Solution for injection is filled in 2 ml Type - I clear glass vial closed with 13 mm grey rubber stopper and 13 mm aluminium flip-off transparent blue seal.

For 5 ml,  
Solution for injection is filled in 5 ml Type - I clear tubular glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip-off transparent blue seal.

For 10 ml,  
Solution for injection is filled in 10 ml Type - I clear tubular glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip-off transparent blue seal.

Pack sizes:

1 × 1 ml vial, 5 × 1 ml vial

1 × 5 ml vial, 5 × 5 ml vial

1 × 10 ml vial

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

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

Prior to use, vials of Cytarabine 100 mg/mL must be warmed to 55°C, for 30 minutes, with adequate shaking, and allowed to cool to room temperature.

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

Water for injections, 0.9% saline or 5% dextrose are commonly used infusion fluids for Cytarabine. Compatibility must be assured before mixing with any other substance.

Infusion fluids containing Cytarabine should be used immediately.

Disposal:

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

#### **7 MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House,  
319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF,  
United Kingdom

#### **8 MARKETING AUTHORISATION NUMBER(S)**

PL 20075/0121

#### **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

15/12/2009

#### **10 DATE OF REVISION OF THE TEXT**

15/12/2009

# Module 3

## Product Information Leaflet



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PACKAGE LEAFLET: INFORMATION FOR THE USER  
**Cytarabine 100 mg/ml Solution for Injection or Infusion**  
 Cytarabine

The name of your medicine is 'Cytarabine 100 mg/ml solution for injection or infusion' but in the rest of the leaflet it will be called 'Cytarabine injection'.

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### In this leaflet:

1. What Cytarabine injection is and what it is used for
2. Before you are given Cytarabine injection
3. How Cytarabine injection is given
4. Possible side effects
5. How to store Cytarabine injection
6. Further information

### 1. What Cytarabine injection is and what it is used for

- Cytarabine injection is used in adults and children. The active ingredient is cytarabine.
- Cytarabine is one of a group of the medicines known as cytotoxics; these medicines are used in the treatment of acute leukaemias (cancer of blood where you have too many white blood cells). Cytarabine interferes with the growth of cancer cells, which are eventually destroyed.
- Cytarabine is also used for the induction and maintenance of remission of leukaemia.
- Remission induction is an intensive treatment to force leukaemia into retreat. When it works, the balance of cells in your blood becomes more normal and your health improves. This relatively healthy spell is called a remission.
- Maintenance therapy is a milder treatment to make your remission last as long as possible. Quite low doses of Cytarabine are used to keep the leukaemia under control and stop it flaring up again.

### 2. Before you are given Cytarabine injection

You should not be given Cytarabine injection

- if are allergic (hypersensitive) to cytarabine, or any of the ingredients of Cytarabine injection.
- if are already taking medicines that have caused you to have a low blood count caused by suppression of your bone marrow (tissue capable of making blood cells).

#### Take Special care with Cytarabine injection

- if your bone marrow is in low state, therapy should be initiated under close medical supervision.
- if you have problems with your liver.
- Cytarabine strongly reduces blood cell production in the bone marrow. This can make you more prone to infections or bleeding. The blood cell numbers can continue to fall for up to a week after stopping treatment. Your doctor will test your blood regularly and examine your bone marrow if required.
- Serious and sometimes life-threatening side effects can occur in the central nervous system, the bowels or lungs.
- Your liver and kidney functions should be monitored during cytarabine therapy. If your liver is not working well before treatment, cytarabine should be given only with utmost care.
- The levels of uric acid (showing that the cancer cells are destroyed) in your blood (hyperuricaemia) may be high during treatment. Your doctor will tell you if you need to take any medicine to control this.

#### Using other medicines

- Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription.
- given medicines containing 5-Fluorocytosine (a medicine used to treat fungal infections).
  - taking medicines containing digoxin or beta-acetyldigoxin, which are used to treat certain heart conditions.
  - taking Gentamicin (an antibiotic used to treat bacterial infections).
  - given medicines containing cyclophosphamide, vinorelbine and prednisone which are used in cancer treatment programmes.

#### Pregnancy and breast-feeding

Avoid becoming pregnant while you or your partner is being treated with Cytarabine. If you are sexually active, you are advised to use effective birth control to prevent pregnancy during treatment, whether you are male or female. Cytarabine may cause birth defects, so it is important to tell your doctor if you think you are pregnant. Men and women have to use effective contraception during and up to 6 months after treatment.

You should stop breast-feeding before starting treatment with Cytarabine because this medicine may be harmful to infants being breast-fed.

Ask your doctor or pharmacist for advice before taking any medicine.

#### Driving and using machines

Cytarabine does not affect your ability to drive or use machinery. However, cancer treatment in general can affect

the ability of some patients to drive or operate machines. If you are affected, you should not drive or use machinery.

### 3. How Cytarabine injection is given

#### Method and routes of administrations

Cytarabine will be given to you by infusion into a vein (through a 'drip') or by injection under the direction of specialists in hospital. Your doctor will decide what dose to give and the number of days' treatment you will receive depending on your condition.

#### Dosage

Based on your condition, your doctor will decide the dose of Cytarabine, whether you are in induction or maintenance therapy and your body surface area. Your body weight and height will be used to calculate your body surface area.

During treatment you will need regular checks including blood tests. Your doctor will tell you how often this should be done. He/she will be making regular checks of:

- Your blood, to check for low blood cell counts that may need treatment.
- Your liver – again using blood tests – to check that Cytarabine is not affecting the way it functions in a harmful way.
- Your kidneys – again using blood tests – to check that Cytarabine is not affecting the way it functions in a harmful way.
- Blood uric acid levels. Cytarabine may increase uric acid levels in the blood. Another medicine may be given if your uric acid levels are too high.

If you are given more Cytarabine injection than you should High doses can worsen side effects like sores in the mouth or may decrease the number of white blood cells and platelets (these help the blood to clot) in the blood. Should this happen, you may need antibiotics or blood transfusions. Mouth ulcers can be treated to make them less uncomfortable as they heal.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

### 4. Possible side effects

Like all medicines, Cytarabine injection can cause side effects, although not everybody gets them.

The side effects of cytarabine are dependent on the dose. The digestive tract is most commonly affected, but also the blood.

Frequencies of side effects are defined using the following convention:

very common	: affects more than 1 user in 10
common	: affects 1 to 10 users in 100
uncommon	: affects 1 to 10 users in 1,000
rare	: affects 1 to 10 users in 10,000
very rare	: affects less than 1 user in 10,000
not known	: frequency cannot be estimated from the available data

The following information is intended for medical or healthcare professionals only

#### Posology and method of administration

By intravenous infusion or injection, or subcutaneous injection. Cytarabine should not be administered by the intrathecal route. Dosage recommendations may be converted from those in terms of bodyweight to those related to surface area by means of nomograms.

#### 1. Remission induction:

##### 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:

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.

#### Children:

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.

#### 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 leucopenia, thrombocytopenia, and anaemia, with appropriate initiation of supportive therapy when indicated.



Common (affects 1 to 10 users in 100):

- fever
- not enough white and red blood cells or blood platelets, which may make you more prone to infections or bleeding
- abnormal blood cells (megaloblastosis)
- loss of appetite
- swallowing difficulty
- belly ache (abdominal pain)
- nausea (feeling sick)
- vomiting
- diarrhoea
- inflammation or ulceration of the mouth or anus
- reversible effects on the skin such as reddening (erythema), blistering, rash, hives, blood vessel inflammation (vasculitis), hair loss
- reversible effects on the liver such as increased enzyme levels
- reversible effects on the eyes such as sore eyes with bleeding (haemorrhagic conjunctivitis) with vision disturbance, sensitivity to light (photophobia), watery or burning eyes and inflammation of the cornea (keratitis)
- reduced consciousness (at high doses)
- speaking difficulties (at high doses)
- abnormal eye movements (nystagmus, at high doses)
- inflammation of the vein at the site of injection
- abnormally high blood uric acid levels (hyperuricaemia)

Uncommon (affects 1 to 10 users in 1,000):

- sore throat
- headache
- serious allergic reactions (anaphylaxis), causing for instance difficulty in breathing or dizziness
- blood-poisoning (sepsis)
- inflammation and ulcers of the gullet
- severe bowel inflammation (necrotising colitis)
- bowel cysts
- ulceration of the skin
- itching
- inflammation at the site of injection
- brown/black spots on the skin (lentigo)
- yellowish skin and eye balls (jaundice)
- lung infection (pneumonia)
- breathing difficulty
- paralysis of the legs and lower body can occur when cytarabine is given into the space surrounding the spinal cord
- muscle and joint pain
- inflammation of the lining that surrounds the heart (pericarditis)
- impaired kidney function
- inability to pass urine (urinary retention)
- chest pain
- burning pain of palms and soles

Very Rare (affects less than 1 user in 10,000):

- inflammation of sweat glands
- irregular heartbeat (arrhythmias)

Other side effects:

The Cytarabine Syndrome may occur 6-12 h after the start of treatment. The symptoms include:

- fever
- bone and muscle pain
- occasional chest pain
- rash
- sore eyes (conjunctivitis)
- nausea (feeling sick)

Your doctor may prescribe corticosteroids (anti-inflammatory medicines) to prevent or treat these symptoms. If they are effective, treatment with cytarabine may be continued.

Central nervous system:

The following symptoms, which are usually reversible, may develop in up to one third of patients after treatment with high cytarabine doses:

- personality changes
- changed alertness
- difficulty in speaking
- problems of coordination
- tremor
- abnormal eye movements (nystagmus)
- headache
- confusion
- sleepiness
- dizziness
- coma
- convulsions

These side effects may occur more often:

- in elderly patients (>55 years of age)
- in patients with impaired liver and kidney functions
- after previous cancer treatment to the brain and spinal cord for instance radiotherapy or injection of cytostatic
- with alcohol abuse

The risk of nervous system damages increases if the cytarabine treatment:

- is given at high doses or at short intervals
- is combined with other treatments that are toxic to the nervous system (such as radiotherapy or methotrexate)

Digestive tract:

Especially in treatment with high doses of cytarabine more severe reactions may appear in addition to the common symptoms. Perforation, death (necrosis) and obstruction of the bowel and inflammation of the inner belly lining have been reported. Liver abscesses, liver enlargement, blockage of liver veins and inflammation of the pancreas have been observed after high-dose therapy.

The side effects on the digestive tract are less if cytarabine is given by infusion.

Lungs:

Acute, distressing breathing difficulties and water in the lungs (pulmonary edema) have been observed, particularly at high doses.

Others:

- heart muscle disease (cardiomyopathy)
- abnormal muscle breakdown (rhabdomyolysis)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. How to store Cytarabine injection

Keep out of the reach and sight of children.

Do not store above 25° C.

Keep the vial in the outer carton in order to protect from light. Do not refrigerate.

Do not use Cytarabine injection after the expiry date on the vial or carton. The expiry date refers to the last day of that month. The product should be used immediately after opening the vial. Do not use Cytarabine injection if you notice that the solution is not clear, colourless and free of particles.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. Further information

What Cytarabine injection contains:

Cytarabine injection contains the active ingredient Cytarabine. 1 ml contains 100 mg Cytarabine.

Each 1 ml vial contains 100 mg of Cytarabine.

Each 5 ml vial contains 500 mg of Cytarabine.

Each 10 ml vial contains 1000 mg of Cytarabine.

The other ingredients are Macrogol 400, Trometamol, and water for injections.

What Cytarabine injection looks like and contents of the pack:

Cytarabine injection is a clear, colourless solution, which is practically free from particles.

Pack sizes:

1 × 1 ml vial, 5 × 1 ml vial

1 × 5 ml vial, 5 × 5 ml vial

1 × 10 ml vial

Not all pack sizes may be marketed.

Marketing Authorisation Holder and manufacturer:

Accord Healthcare Limited,  
Sage House, 319 Pinner Road, North Harrow, Middlesex,  
HA1 4HF, United Kingdom.

The leaflet was last approved in 11/2009.

## Incompatibilities

Incompatibilities with: Heparin, insulin, Methotrexate, 5-fluorouracil, nafcillin, oxacillin, penicillin G, and methyl-prednisolone succinate.

## Instruction for Use/Handling

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

Prior to use, vials of Cytarabine 100 mg/mL must be warmed to 55°C, for 30 minutes, with adequate shaking, and allowed to cool to room temperature.

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

Water for injections, 0.9% saline or 5% dextrose are commonly used infusion fluids for Cytarabine. Compatibility must be assured before mixing with any other substance. Infusion fluids containing Cytarabine should be used

immediately.

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

Shelf life

2 years

Chemical and physical in-use stability after dilution with sodium chloride injection (0.9 % w/v) and dextrose injection (5% w/v)

indicate that after dilution with recommended intravenous fluids, Cytarabine Injection remains stable for 24 hours at temperature below 25° C and 72 hours at 2-8°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° C, unless dilution has taken place in controlled and validated aseptic conditions.

Storage

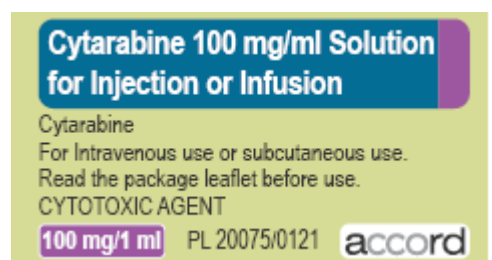
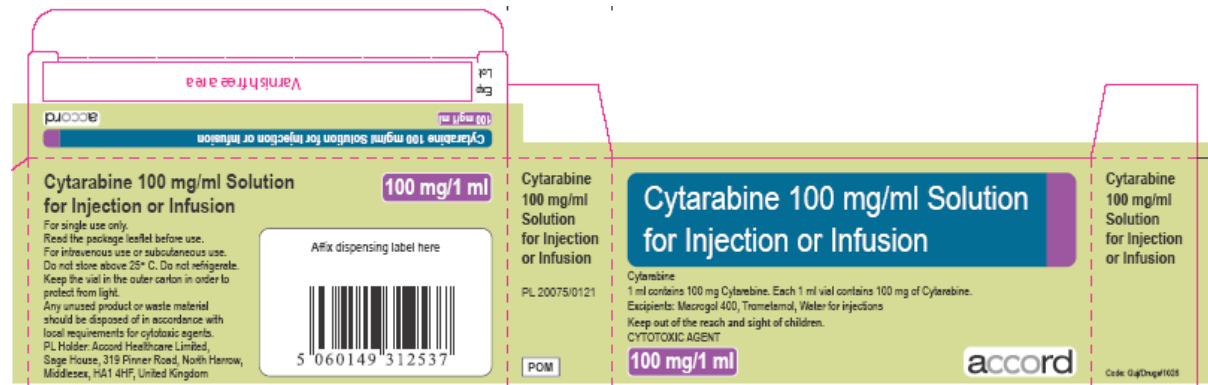
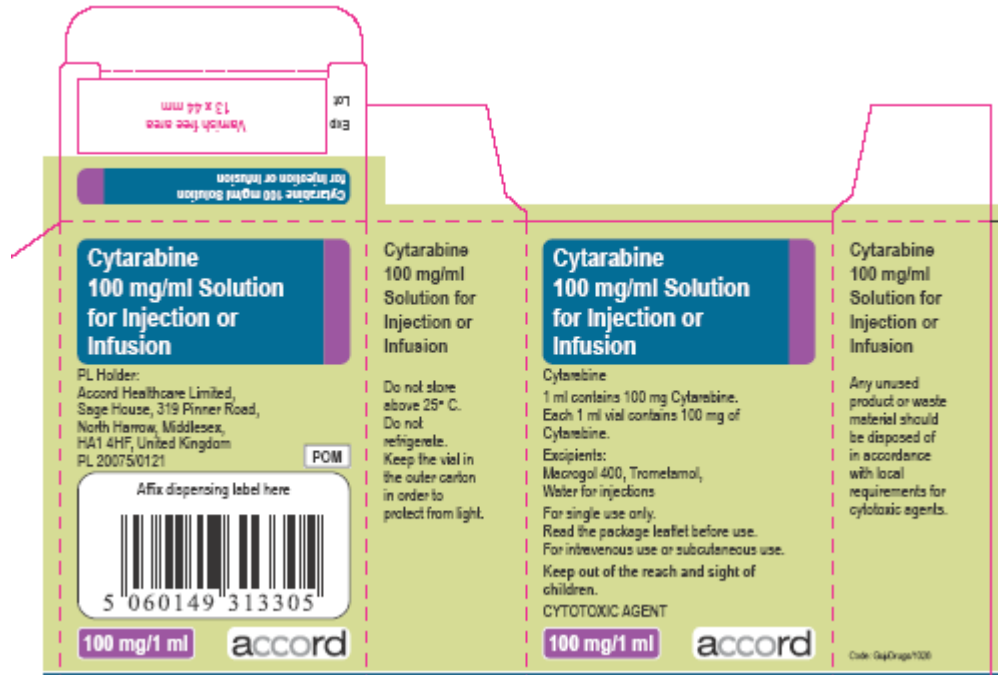
Do not store above 25° C.

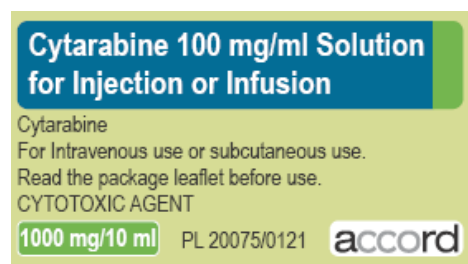
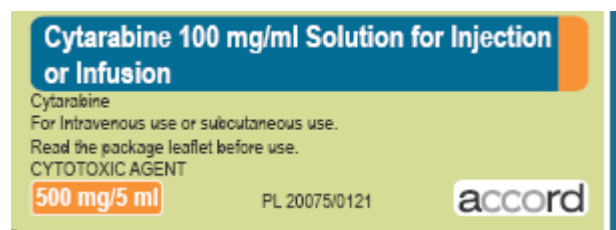
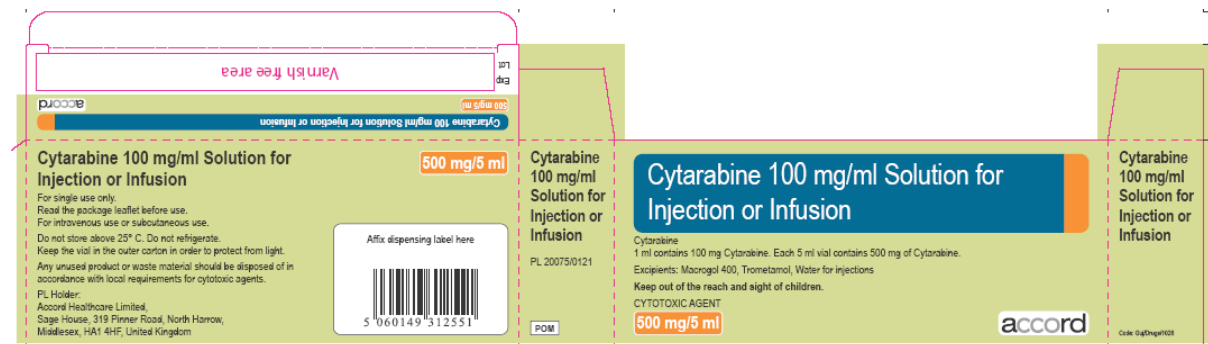
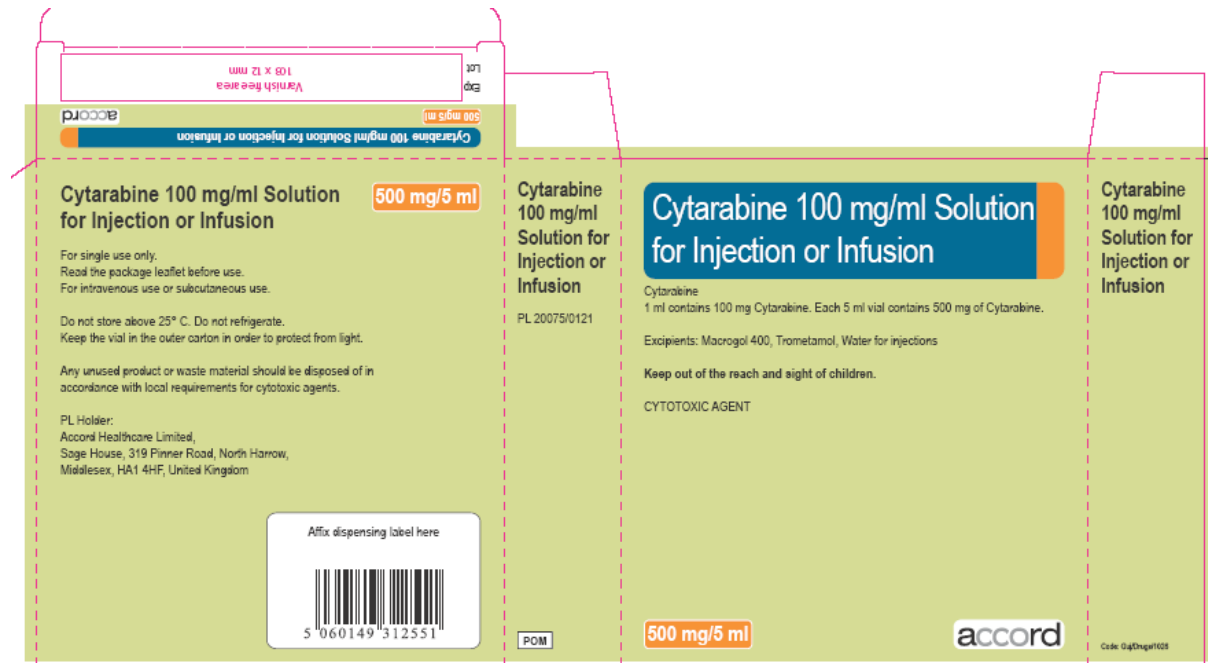
Keep the vial in the outer carton in order to protect from light.

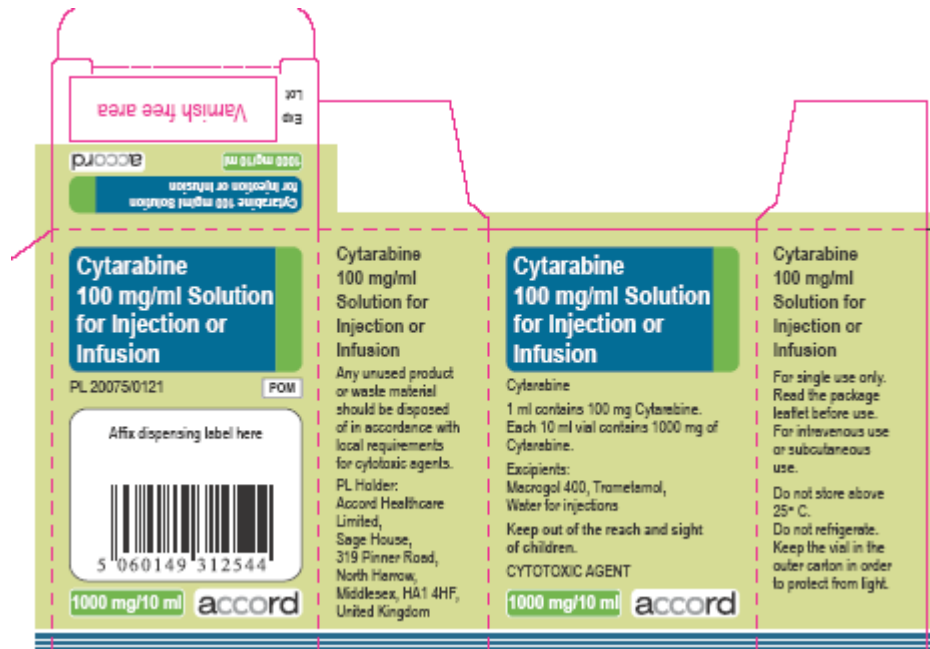
Do not refrigerate.

# Module 4 Labelling

## Cytarabine 100mg/ml Solution for Injection or Infusion







## Module 5

### Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Cytarabine 100mg/ml Solution for Injection or Infusion, used in the treatment of acute myeloid leukaemia in adults and for other acute leukaemias, is approvable.

This is an application submitted under Article 10(1) of Directive 2001/83 (as amended) for Cytarabine 100mg/ml Solution for Injection. It has been shown to be a generic medicinal product of the originator product Cytarabine 100mg/ml Solution for Infusion or Injection (Marketing Authorisation Holder: Pharmacia Limited) which was granted a licence in the UK on 3<sup>rd</sup> June 1999; hence the 10 year rule is fulfilled.

Cytarabine is a pyrimidine nucleoside and S-phase specific antineoplastic agent, which inhibits the synthesis of deoxyribonucleic acid. Cytarabine is metabolised by deoxycytidine kinase to 5'- mononucleotide (AraCMP). Detailed studies on the mechanism of cytotoxicity in vitro suggest that the primary action of Cytarabine is inhibition of deoxycytidine synthesis. Inhibition of cytidylic kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytotoxic actions. In light of the S-phase specificity, the drug is highly sequence-dependent and may be given either by continuous infusion or intermittently. Cytarabine is commonly used to treat AML. Side effects include myelosuppression, nausea, hyperuricaemia, neurotoxicity, The Cytarabine Syndrome and stomatitis.

The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, pre-clinical and clinical overviews have been submitted.

A formal *Environment Assessment* was not submitted. This is acceptable as no increase in environmental risk is to be expected compared to that of the reference product.

No *Risk Management Plan* other than the documentation of the Pharmacovigilance system has been provided. The Applicant has supplied a justification for not submitting a European Risk Management Plan and this is satisfactory.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

Since a literature review has been presented for the Non-clinical Overview, it is not known whether the studies cited were conducted in accordance with the GLP regulations. However, it is assumed that the studies conducted by the innovator would have been in compliance with the standards prevailing at the time.

No new clinical study was submitted.

The patient information leaflet (PIL) is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and

organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

## II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Cytarabine 100mg/ml Solution for Injection or Infusion
Name(s) of the active substance(s) (INN)	Cytarabine
Pharmacotherapeutic classification (ATC code)	L01BC01: Pyrimidine analogue
Pharmaceutical form and strength(s)	100 mg/ml solution for injection or infusion
Reference numbers for the Mutual Recognition Procedure	UK/H/1641/001/DC
Reference Member State	United Kingdom
Member States concerned	Bulgaria, Estonia, Latvia and Lithuania
Marketing Authorisation Number(s)	PL 20075/0121
Name and address of the authorisation holder	Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex HA1 4HF UK

### III SCIENTIFIC OVERVIEW AND DISCUSSION

#### III.1 QUALITY ASPECTS

##### DRUG SUBSTANCE

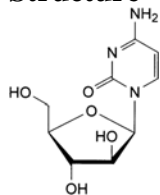
##### Cytarabine

##### General Information

##### Nomenclature

Name: Cytarabine

##### Structure



Description: White or almost white crystalline powder

Molecular formula:  $C_9H_{13}N_3O_5$

Relative molecular mass: 243.22

There is a Ph Eur monograph for the drug substance, cytarabine.

##### Manufacture

A satisfactory Ph Eur Certificate of Suitability (CEP) has been provided which covers the manufacture and control of the drug substance cytarabine. Additional tests for related substances and residual solvents have been described and are in line with ICH guidelines.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Cytarabine drug substance is stored in appropriate packaging that comply with Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs. Specifications and certificates of analysis have been provided.

Batch analysis data have been provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

The finished product manufacturer routinely tests each batch of the drug substance in accordance with a satisfactory specification upon receipt.

Appropriate stability data have been generated for the drug substance and supports an appropriate retest period when stored in the proposed packaging.

##### DRUG PRODUCT

##### Other ingredients

Other ingredients consist of pharmaceutical excipients, namely macrogol 400, trometamol and water for injections. An appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph.Eur monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

There were no novel excipients used and no overages.

### **Pharmaceutical Development**

The objective of development activities was to achieve a stable formulation of cytarabine 100mg/ml similar to the reference product cytarabine 100mg/ml, manufactured by Pharmacia Limited.

### **Compatibility**

Compatibility studies have demonstrated that the product is compatible with the proposed packaging component and rubber stoppers. Container integrity is demonstrated and is satisfactory.

### **Impurity Profiles**

Comparative impurity profiles between the test product and a German authorised product 'ARA-cell', which is equivalent to the UK reference product, have been provided and are satisfactory.

### **Manufacture**

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation data for two commercial batches have been provided which are satisfactory. All data are within specifications.

### **Finished product specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

### **Container Closure System**

The finished product is filled into colourless neutral Type I glass vials and sealed with chlorobutyl rubber stopper with aluminium flip-off seals.

For 1 ml,

Solution for injection is filled in 2 ml Type - I clear glass vial closed with 13 mm grey rubber stopper and 13 mm aluminium flip-off transparent blue seal with pack sizes of 1x1ml vial, 5x1ml vials.

For 5 ml,

Solution for injection is filled in 5 ml Type - I clear tubular glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip-off transparent blue seal with pack sizes of 1x5ml vial and 5x5ml vial.

For 10 ml,  
Solution for injection is filled in 10 ml Type - I clear tubular glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip-off transparent blue seal in pack size of 1 x 10ml vials.

All primary product packaging complies with EU legislation regarding contact with food.

Satisfactory specifications and certificates of analysis are provided. Satisfactory declaration has been provided by the suppliers of all packaging materials comply with the EC Directed 2002/72 as well as with the relevant Ph Eur monograph for containers.

### **Stability**

Stability studies were performed on three batches of each presentation of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years for unopened product with the storage conditions “Do not store above 25° C”, “Keep the vial in the outer carton in order to protect from light” and “Do not refrigerate”.

The shelf-life of the injection *in-use* is “Chemical and physical in-use stability has been demonstrated in sodium chloride injection (0.9 % w/v) and dextrose injection (5% w/v) for up to 24 hours at temperature below 25° C and for up to 72 hours at 2-8°C”.

General storage conditions for the product in use are “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° C, unless dilution has taken place in controlled and validated aseptic conditions”.

### **Conclusion**

It is recommended that a Marketing Authorisation is granted for this application.

The requirements for a generic product of the proposed and originator products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and reference products.

## **2 NON-CLINICAL ASSESSMENT**

### **2.1. Critical evaluation of the Non-Clinical Overview**

The pharmacological, pharmacokinetic and toxicological properties of cytarabine are well known. As cytarabine is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The non-clinical overview has been written by a suitably qualified person. The overview cites 58 references from the published literature dated up to 2007 and is satisfactory.

### **2.2 Conclusions**

There are no objections to approval of Cytarabine Injection 100mg/ml solution for injection or infusion.

### III.3 CLINICAL ASPECTS

#### INTRODUCTION

Cytarabine is a pyrimidine nucleoside and S-phase specific antineoplastic agent, which inhibits the synthesis of deoxyribonucleic acid. Cytarabine is metabolised by deoxycytidine kinase to 5'-mononucleotide (AraCMP). Detailed studies on the mechanism of cytotoxicity in vitro suggest that the primary action of Cytarabine is inhibition of deoxycytidine synthesis. Inhibition of cytidylic kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytotoxic actions. In light of the S-phase specificity, the drug is highly sequence-dependent and may be given either by continuous infusion or intermittently. Cytarabine is commonly used to treat AML. Side effects include myelosuppression, nausea, hyperuricaemia, neurotoxicity, The Cytarabine Syndrome and stomatitis.

#### *Therapeutic Indications*

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

The proposed indications are consistent with the approved UK reference SmPC.

#### *Posology and method of administration*

By intravenous infusion or injection, or subcutaneous injection.

**Cytarabine should not be administered by the intrathecal route.**

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

#### **1. Remission induction:**

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:

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.

### ***Children:***

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.

### ***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 leucopenia, thrombocytopenia, and anaemia, with appropriate initiation of supportive therapy when indicated.

The proposed posology is consistent with the approved UK reference SmPC.

The clinical overview report covers the product rationale, overview of biopharmaceutics, pharmacology, efficacy, safety and benefits and risks conclusions and is written by a suitably qualified expert. The report refers to 64 publications up to the year 2008.

## **3.2 Clinical study reports**

No new data have been submitted and none are required for this generic application.

Cytarabine 100 mg/ml solution for injection or infusion is the generic version of Cytarabine 100 mg/ml solution for injection (Pharmacia, UK). The use of the reference product is well-established in the EU. .

According to CPMP guidelines, the Applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

### **3.2.1 Pharmacodynamic studies**

No new data have been submitted and none are required for this application.

The pharmacodynamic and pharmacokinetic claims in the SmPC are consistent with the innovator product. The pharmacodynamic and pharmacokinetic properties have been extensively studied in the past.

### **3.2.2 Additional data**

Cytarabine is indicated for induction of remission in acute myeloid leukaemia in adults and for other acute leukaemias of adults and children.

Satisfactory evidence to support the proposed indication has been provided in the clinical overview (e.g. Yee et al., 2004; Bahng H et al., 2001; Palmieri S et al., 2002).

Cytarabine has an acceptable adverse events profile. No novel safety data are supplied or required for this generic application. The Applicant has provided a review of the published

literature, confirming the safety of Cytarabine (HSDB: Hazardous Substance Data Bank: National Library of Medicine).

#### **4 Post marketing experience**

No post-marketing data is available. The medicinal product has not been marketed in any country.

Cytarabine has a well-recognised efficacy and an acceptable level of safety in the indications approved for the reference product, and corresponding products have been widely used in many countries.

#### **5 Benefit-Risk assessment**

The application contains an adequate review of published clinical data. Approval is recommended from the clinical point of view.

#### **Summary of Product Characteristics**

This is satisfactory.

#### **Patient Information Leaflet and Labels**

These are satisfactory.

#### **CONCLUSIONS**

The efficacy and safety of the product are satisfactory for the grant of a product licence.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The important quality characteristics of Cytarabine 100mg/ml Solution for Injection or Infusions are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for applications of this type.

### **EFFICACY**

No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arise from this application.

The SmPC and PIL are satisfactory and consistent with that for the reference product.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with cytarabine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>
07/01/2010	Information Update	Information update created as changes were made to the dimensions of the labelling mock-ups	Approved