Public Assessment Report

Decentralised Procedure

Cytarabine 100 mg/ml Solution for Injection or Infusion

Cytarabine

UK/H/4353/001/DC

UK licence no: PL 18727/0024

FRESENIUS KABI ONCOLOGY PLC
Cytarabine 100 mg/ml Solution for Injection or Infusion

PL 18727/0024

LAY SUMMARY

On 10th May 2012, the CMSs and the RMS agreed to grant a marketing authorisation to Fresenius Kabi Oncology plc for the medicinal product Cytarabine 100 mg/ml Solution for Injection or Infusion. The marketing authorisation was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 25th June 2012.

Cytarabine is used in adults and children. The active ingredient is 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 cells, which are eventually destroyed.

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 period 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.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Cytarabine 100 mg/ml Solution for Injection or Infusion outweigh the risks, hence a Marketing Authorisation was granted.
## TABLE OF CONTENTS

Module 1: Information about initial procedure Page 3

Module 2: Summary of Product Characteristics Page 5

Module 3: Patient Information Leaflets Page 18

Module 4: Labelling Page 24

Module 5: Scientific Discussion Page 27

1 Introduction
2 Quality aspects
3 Non-clinical aspects
4 Clinical aspects
5 Overall conclusions

Module 6 Steps taken after initial procedure
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Cytarabine 100 mg/ml Solution for Injection or Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10.1</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Cytarabine</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Solution for Injection or Infusion</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>100 mg/ml</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Fresenius Kabi Oncology Plc</td>
</tr>
<tr>
<td></td>
<td>Lion Court, Farnham Road, Bordon, Hampshire</td>
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<td></td>
<td>GU35 0NF</td>
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<td></td>
<td>United Kingdom</td>
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<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
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<td><strong>CMSs</strong></td>
<td>Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Iceland, Italy, Lithuania, Luxemburg, Latvia, Malta, Norway, Poland, Portugal, Romania, Spain, Sweden, Slovak Republic and The Netherlands</td>
</tr>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/4353/001/DC</td>
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<tr>
<td><strong>Timetable</strong></td>
<td>Day 210: 10th May 2012</td>
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</table>
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
Each ml of solution contains 100 mg of cytarabine.

Each 1 ml vial contains 100 mg of cytarabine.

Each 5 ml vial contains 500 mg of cytarabine.

Each 10 ml vial contains 1 g of cytarabine.

Each 20 ml vial contains 2 g of cytarabine.

Excipients:
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for Injection or Infusion.

clear, colourless solution.

pH- 7.0 - 9.5

Osmolarity: 250 to 400 mOsm/L

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
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.

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

Cytarabine 100 mg/ml should not be administered by the intrathecal route.

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/m²). Dose recommendation may be converted from those in terms of bodyweight to those related to surface area by means of nomograms.

1) Remission induction:
Induction therapy dosage and schedule vary depending on the regimen used.

a) Continuous treatment:

The following dose regimens have been used for continuous treatment in remission induction.

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:

The following dose regimens have been used for intermittent treatment in remission induction.

1) **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.

ii) **Cytarabine 100-200 mg/m² /24 hours**, as continuous infusion for 5-7 days alone or in 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.

2) Maintenance therapy:

Maintenance dosage and schedule vary depending on the regimen used.

The following dose regimens have been used for continuous treatment following remission induction.

i) 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.

ii) Cytarabine has also been administered in doses of **100-200 mg/m²**, as continuous infusion for 5 days at monthly intervals as monotherapy or in combination with other cytostatics.

**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 hematological and non-hematological toxicity. Also refer to precautions (4.4) for treatment stopping requirements.

**Paediatric patients:**

Safety in infants has been not established.

**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.

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

4.3 Contraindications
- Hypersensitivity to the cytarabine or to any of the excipients of cytarabine injection.
- Anaemia, leucopenia and thrombocytopenia of non-malignant aetiology (e.g bone marrow aplasia); unless the clinician feels that such management offers the most hopeful alternative for the patient.
- Degenerative and toxic encephalopathies, especially after the use of methotrexate or treatment with ionizing radiation.

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. 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. 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:
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 leukemia.

Patients treated with high doses of cytarabine should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders.

Severe and sometimes fatal pulmonary toxicity, adult respiratory distress syndrome and pulmonary oedema have occurred following 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 intravenous cytarabine at conventional doses in combination with other drugs.

Both hepatic and renal function should be monitored during cytarabine therapy. In patients with pre-existing liver impairment cytarabine should be administered only with utmost care.

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

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.

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

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

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

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.

Due to immunosuppressive action of cytarabine Infection - 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.

4.6 Fertility, Pregnancy and lactation

Pregnancy:

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

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 breast-feeding.

Fertility:
Fertility studies to assess the reproductive toxicity of cytarabine have not been conducted. Gonadal suppression, resulting in amenorrhea or azoospernia, may occur in patients taking cytarabine therapy, especially in combination with the alkylating agents. In general, these effects appear to be related to dose and length of therapy and may be irreversible (see section 4.8). 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 a reliable contraceptive method.

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)

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.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>MedDRA Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>Sepsis (immunosuppression), cellulitis at injection site</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and</td>
<td>Uncommon</td>
<td>Lentigo</td>
</tr>
<tr>
<td>unspecified (including cysts and polyps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td>Common</td>
<td>Anaemia, megaloblastosis, leucopenia, thrombocytopenia</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>Common</td>
<td>Anorexia, hyperuricaemia</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>At high doses cerebellar or cerebral influence with deterioration of the level of consciousness, dysarthria, nystagmus</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>headache, peripheral neuropathy</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Common</td>
<td>Reversible haemorrhagic conjunctivitis (photophobia, burning, visual disturbance, increased lacrimation), keratitis</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>MedDRA Term</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Very rare</td>
<td>Arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>Pneumonia, dyspnea, sore throat</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Dysphagia, abdominal pain, nausea, vomiting, diarrhoea, oral / anal inflammation or ulceration</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Esophagitis, esophageal ulceration, pneumatosis cystoides intestinalis, necrotising colitis, peritonitis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Common</td>
<td>Reversible effects on the liver with increased enzyme levels</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Reversible undesirable effects to the skin, such as erythema, bullous dermatitis, urticaria, vasculitis, alopecia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Skin ulceration, pruritus, burning pain of palms and soles</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Neutrophilic eccrine hidradenitis</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon</td>
<td>Myalgia, arthralgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Renal impairment, urinary retention</td>
</tr>
<tr>
<td>General disorders and administration site Conditions</td>
<td>Common</td>
<td>Fever, thrombophlebitis at the injection site</td>
</tr>
</tbody>
</table>

*Cytarabine (Ara-C) Syndrome: (Immunoallergic effect):*
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.

Adverse effects due to high dose cytarabine treatment, other than those seen with conventional doses include:

**Hematological toxicity:**
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, 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.
Corneal and conjunctival toxicity:
Reversible lesion of corneal and haemorrhagic conjunctivitis have been described. These phenomena can be prevented or decreased by installation od corticosteroid eye drops.

Gastrointestinal disorders:
Especially in treatment with high doses of cytarabine, more severe reactions may appear in addition to common symptoms. Intestinal perforation or necrosis with ileus and peritonitis have been reported.

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

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.

Amenorrhoea and azoospermia (sec section 4.6)

4.9 Overdose
No specific antidote. Managed advised at overdosage include: Cessation of therapy, followed by management of ensuing bone marrow depression including whole blood or platelet transfusion and antibiotics as required. Twelve doses of 4.5 g/m² by IV infusion over one hour every 12 hours induces irreversible and fatal central nervous system toxicity.

Cytarabine may be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antineoplastic agents, pyrimidine analogue
ATC code: L01BC01

Cytarabine, a pyrimidine nucleoside analogue, is an antineoplastic agent which inhibits the synthesis of deoxyribonucleic acid 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 triphosphosphate 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 cytoidal actions.

High dose cytarabine regimes can overcome the resistance of leukemic 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 coorelation between intracellular retention of ARA-CTP and percentage of cells in S-phase.

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 inactive deaminated product, arabinofuranosyl uracil (ARA-U). Cytarabine appears to be metabolised rapidly, primarily by the liver and perhaps by the kidney. After single high intravenous doses, blood levels fall to unmeasurable levels within 15 minutes in most patients. Some patients have indemonstrable circulating drug as early as 5 minutes after injection. 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/m² cytarabine intravenous infusion, are around 100-300 nanograms/ml. Peak plasma levels are achieved about 20-60 minutes after subcutaneous application. At comparable doses, they are significantly lower than the plasma levels achieved after intravenous administration.

5.3 Preclinical safety data
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
Hydrochloric Acid (for pH-adjustment)
Sodium Hydroxide (for pH-adjustment)
Water for injections

6.2 Incompatibilities
Solutions of Cytarabine have been reported to be incompatible with various drugs, i.e. carbenicillin sodium, cephalothin sodium, fluorouracil, gentamicin sulphate, heparin sodium, hydrocortisone sodium succinate, 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 products excepts those mentioned in section 6.6.

6.3 Shelf life
18 months

After first opening:
After first opening, product should be used immediately.

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

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

6.4 Special precautions for storage
Do not store above 25 °C. Do not refrigerate or freeze.

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

6.5 Nature and contents of container
For 1 ml,
Solution for injection is filled in 2 ml Type - I colourless glass vial closed with bromobutyl rubber stopper, and sealed with green aluminium flip off overseal.

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

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

For 20 ml,
Solution for injection is filled in 20 ml Type - I colourless glass vial closed with bromobutyl rubber stopper, and sealed with yellow aluminium flip off overseal.
The package contains 1 vial of 1 ml, 5 ml, 10 ml and 20 ml, respectively.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

For single use only.

Cytarabine is intended for intravenous or subcutaneous use only.

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

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

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

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

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

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

**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.

Infusion fluids containing cytarabine should be used immediately.

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**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):**

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

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

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

Pregnant personnel are advised not to handle chemotherapeutic agents.

**Contamination:**

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.

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

**Disposal:**

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

Any unused product or waste material should be disposed of in accordance with local requirements.
8  MARKETING AUTHORISATION NUMBER(S)
    PL 18727/0024

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
    25/06/2012

10  DATE OF REVISION OF THE TEXT
    25/06/2012
PAR Cytarabine 100 mg/ml Solution for Injection or Infusion

UK/H/4353/001/DC

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER
Cytarabine 100 mg/ml solution for injection or infusion

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 any further questions, please ask your doctor or pharmacist.
- If any of the side effects gets worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. WHAT CYTARABINE IS AND WHAT IT IS USED FOR

Cytarabine is used in adults and children. The active ingredient is cytarabine.

Cytarabine is one of a group of medicines known as cytosine, these medicines are used in the treatment of acute leukaemia (cancer of blood cells) which can occur in children and adults.

Emission of anticancer is an intensive treatment to those leukaemia into remission. When it works, the balance of cells in your body becomes normal and your health improves. This relatively better life is called a remission.

Maintain in treatment is a little treatment to keep your remission lasts as long as possible. Quite low doses of cytara are used to keep the remission under control and stop it flaring up again.

2. BEFORE YOU ARE GIVEN CYTARABINE

Do not use cytara if you:
- are allergic (hypersensitive) to cytarabine, or any of the other ingredients of Cytarabine.
- have kidney problems or abnormal blood tests.
- have heart problems or abnormal blood tests.
- have a history of leukaemia.
- have liver problems or abnormal blood tests.
- have a history of bleeding or clotting disorders.

If any of these effects are serious, tell your doctor immediately.

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4. POSSIBLE SIDE EFFECTS

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

The side effects of Cytarabine depend on the dose. The amount of treatment is not common, but they are also due to the disease.

Common: may affect 1 in 10 people
- fever
- nausea and vomiting
- diarrhea
- abnormal weight loss

Uncommon: may affect up to 1 in 100 people
- sore throat
- headache
- abnormal reactions (anaphylaxis), causing for instance difficulty in breathing or dizziness
- bleeding tendency
- inflammation and abscess of the gallway

You should be aware that these symptoms are likely to improve after treatment.

You can stop using Cytarabine if any of these effects are serious, tell your doctor immediately.

5. HOW TO USE CYTARABINE

Method and route of administration:

Cytarabine will be given to you by infusion into a vein (through a drip) or by injection under the direction of your doctor in hospital.

You will need to be in hospital during treatment. You should be able to continue your normal daily activities during treatment. You will receive treatment for as long as your doctor thinks it is necessary.

Dosage:

The dosage and frequency will be decided for the individual patient, depending on the type of treatment, the stage of your disease, and the response to treatment.

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PAR Cytarabine 100 mg/ml Solution for Injection or Infusion

UK/H/4353/001/DC

- severe headache (including collapse)
- fever
- destruction of skin
- itching
- inflammation at the site of injection
- bruising (including the site of injection)
- yellow disc or yellow discoloration of nail
- long-lasting fever
- breathing difficulty
- pain and pressure
- inflammation of the heart: heart failure
- impaired kidney function
- inability to produce urine (renal failure)
- chest pain
- burning pain of palm and soles
- Very rare: type 2 diabetes in people
- inflammation of bones
- irregular heartbeat (arrhythmia)

Other side effects:
The cytarabine plasma half-life occurs 6-12 hours after the start of treatment. The symptoms include:
- fever
- bone and muscle pain
- occasional diarrhea
- rash
- acne
- changes in vision

These symptoms may arise for several days to a few weeks due to the high levels of cytarabine in the blood.

Central nervous system:
The following symptoms, which are usually reversible, may develop up to one-third of patients after treatment with high doses of cytarabine:
- personality change
- confusion
- difficulty in concentrating
- problems with coordination
- sleep disturbance
- abnormal eye movement

- headache
- convulsion
- dizziness
- disorders of vision
- cramps

Other side effects include:

- these side effects may occur more often
- in elderly patients (55 years of age)
- with impaired liver and kidney function
- after previous cancer treatment to the brain and spinal cord
- with alcohol abuse
- the risk of severe allergy increases with the cytarabine treatment.

Dose-related effects:
- the side effects of cytarabine are dose-dependent and include:
- fever
- bone and muscle pain
- occasional diarrhea
- rash
- acne
- changes in vision

6. FURTHER INFORMATION

What Cytarabine contains:
The active ingredient is cytarabine.
Each ml of solution contains 100 mg of cytarabine.
The 10 ml ampoule contains 100 mg of cytarabine.
The 1 ml vial contains 100 mg of cytarabine.
The 10 ml vial contains 1 g of cytarabine.
The 2 ml vial contains 2 g of cytarabine.
The other ingredients are hydrochloric acid, sodium hydroxide and water for injections.

What Cytarabine looks like and contents of the pack:
The medicinal product is presented as a clear, colourless solution for parenteral infusion. The active substance is presented in a clear, colourless plastic vial with a metal flip-off cap (glass 2 ml, polyethylene 6 or 10 ml) and polypropylene 20 ml.
The pack contains 1 x 1 ml, 1 x 5 ml, 1 x 10 ml and 20 ml of 1 ml, respectively.
For all packs sizes may be mentioned.

Marketing Authorisation Holder and Manufacturer:
Levercott, Penhale Road, Exeter,
Exeter, EX1 3DJ
United Kingdom

This medicinal product is authorised in the Member States of the EEA under the following names:

Belgium
Cytarabine Pharmaco Kids 100 mg/ml Cytarabine per injection

China
Cytarabine Kids (100 mg/ml sterilized water)

Denmark
Cytarabine Pharmaco Kids 100 mg/ml Injection per infusion

Germany
Cytarabine Kids 100 mg/ml sterilized water

India
Cytarabine Pharmaco Kids 100 mg/ml Injection per infusion

Finland
Cytarabine Pharmaco Kids 100 mg/ml sterilized water

France
Cytarabine Pharmaco Kids 100 mg/ml Injection per infusion

Latvia
Cytarabine Pharmaco Kids 100 mg/ml Injection per infusion

Netherlands
Cytarabine Pharmaco Kids 100 mg/ml Injection per infusion

Norway
Cytarabine Pharmaco Kids 100 mg/ml Injection per infusion

Switzerland
Cytarabine Pharmaco Kids 100 mg/ml Injection per infusion

Turkey
Cytarabine Kids 100 mg/ml Injection per infusion

This leaflet was last reviewed on: 08/2012

16
Module 4

Labelling

For i.v or s.c use only. For single use only.

100 mg/1 ml Cytarabine 100 mg/ml Solution for Injection or Infusion

Cytotoxic agent

1 ml

200% 40 x 18 mm
Cytarabine 100 mg/ml Solution for Injection or Infusion

100 mg/1 ml
100 mg/1 ml

Each ml of solution contains 100 mg of cytarabine.

Contains hydrochloric acid, sodium hydroxide and water for injections. See the package leaflet for further information.

Read the package leaflet before use.

For single use only.

Keep out of the reach and sight of children.

Read the leaflet for the shelf life of the diluted product.

Do not store above 25°C.

Do not refrigerate or freeze.

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

Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road, Bordon Hampshire, GU35 0NF
United Kingdom
PAR Cytarabine 100 mg/ml Solution for Injection or Infusion

For i.v or s.c use only.
For single use only.

500 mg/5 ml
Cytarabine 100 mg/ml
Solution for Injection or Infusion

Cytotoxic agent
For intravenous use or subcutaneous use only.
One vial

Each ml of solution contains 100 mg of cytarabine.

Contains hydrochloric acid, sodium hydroxide and water for injections. See the package leaflet for further information.

Read the package leaflet before use.
For single use only.
Keep out of the reach and sight of children.
Do not store above 25°C.
Do not refrigerate or freeze.

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

Plesan Kabi Oncology Plc, Lion Court, Fairham Road, Bordon Hampshire, GU35 0NF United Kingdom

Pantone 485 C

200% 60 x 18 mm
PAR Cytarabine 100 mg/ml Solution for Injection or Infusion

**For i.v or s.c use only.**

**For single use only.**

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

**Cytotoxic agent**

Each ml of solution contains 100 mg of cytarabine.

Contains hydrochloric acid, sodium hydroxide and water for injections.

See the package leaflet for further information.

Read the package leaflet before use.

For single use only.

Keep out of the reach and sight of children.

Read the leaflet for the shelf life of the diluted product.

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

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

Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road,
Bordon, Hampshire, GU35 0NP
United Kingdom
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Cytarabine 100 mg/ml Solution for Injection or Infusion in the treatment of acute leukaemia could be approved.

This application was submitted under Article 10.1, claiming to be generic medicinal product of Cytarabine 100 mg/ml Solution for Injection or Infusion (European Reference Product), which was first licensed in the UK to Pharmacia Ltd, on 3rd June 1999.

With UK as the RMS in this Decentralised Procedure (UK/H/4353/001/DC), Fresenius Kabi Oncology Plc applied for the Marketing Authorisation for Cytarabine 100 mg/ml solution for injection or infusion in the following CMSs:

Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Iceland, Italy, Lithuania, Luxemburg, Latvia, Malta, Norway, Poland, Portugal, Romania, Spain, Sweden, Slovak Republic and The Netherlands

Cytarabine, a pyrimidine nucleoside analogue, is an antimetabolite antineoplastic that inhibits DNA synthesis. Its actions are specific for the S phase of the cell cycle. It also has antiviral and immunosuppressant properties. 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 cytocidal 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 used in the treatment of acute myeloid leukaemia, and is used in regimens for consolidation in patients with acute lymphoblastic leukaemia. Cytarabine has also been administered intrathecally in the treatment of meningeal leukaemia.

No new clinical or non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of the originator product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within and outside the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for the non-submission of a Risk Management Plan.
All member states agreed to grant a licence for the above product at the end of the procedure (Day 210 – 10th May 2012). After a subsequent national phase, the UK granted a licence for this product on 25th June 2012 (PL 18727/0024).
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Cytarabine 100 mg/ml Solution for Injection/Infusion |
| Name(s) of the active substance(s) (USAN) | Cytarabine |
| Pharmacotherapeutic classification (ATC code) | Anti-metabolite (Pyrimidine analogues) ATC code: L01BC01 |
| Pharmaceutical form and strength(s) | Solution for Injection/Infusion, 100 mg/ml |
| Reference numbers for the Decentralised Procedure | UK/H/4353/001/DC |
| Reference Member State | United Kingdom |
| Concerned Member States | Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Iceland, Italy, Lithuania, Luxemburg, Latvia, Malta, Norway, Poland, Portugal, Romania, Spain, Sweden, Slovak Republic and The Netherlands |
| Marketing Authorisation Number(s) | PL 18727/0024 |
| Name and address of the authorisation holder | Fresenius Kabi Oncology Plc Lion Court, Farnham Road, Bordon, Hampshire, GU35 0NF United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Cytarabine

Chemical Names: 4-amino-1-[(2R,3S,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2-one

Structure:

\[
\begin{align*}
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\text{O} & \\
\text{O} & \\
\text{OH} & \\
\end{align*}
\]

Molecular formula: C₉H₁₃N₃O₅

Molecular weight: 243.22

Physical form: White or almost white, crystalline powder.

Cytarabine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance cytarabine are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients hydrochloric acid, sodium hydroxide and water for injection.

All excipients comply with the relevant European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the pharmaceutical development programme was to obtain a stable product containing cytarabine that could be considered generic medicinal product of Cytarabine 100 mg/ml Solution for Infusion or Injection (Pharmacia Ltd, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparative impurity profiles have been provided for the proposed and originator products.

Manufacture

Satisfactory batch formulae have been provided for the manufacture of the products, along
with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

**Finished Product Specifications**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The finished product is supplied in:

For 1 ml,
Solution for injection is filled in 2 ml Type - I colourless glass vial closed with bromobutyl rubber stopper, and sealed with green aluminium flip off overseal.

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

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

For 20 ml,
Solution for injection is filled in 20 ml Type - I colourless glass vial closed with bromobutyl rubber stopper, and sealed with yellow aluminium flip off overseal.

The package contains 1 vial of 1 ml, 5 ml, 10 ml or 20 ml, respectively.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with relevant guidelines.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 18 months for unopened vials has been set, with storage conditions “Do not store above 25 °C” and “Do not refrigerate or freeze”.

**After first opening:**
After first opening, the product should be used immediately.

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

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

**Bioequivalence/bioavailability**
No bioequivalence studies have been submitted and none are required to support an application of this type.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SPC, PIL and labelling are pharmaceutically satisfactory.

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for Oxaliplatin 5 mg/ml Concentrate for solution for infusion. The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

The marketing authorisation holder has stated that not all packs are intended to be marketed. However, they have committed to submitting mock-ups of any pack size to the relevant regulatory authorities before marketing.

**Marketing Authorisation Application (MAA) Form**
The MAA form is pharmaceutically satisfactory.

**Expert Report**
A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
There are no objections to the approval of this product from a pharmaceutical point of view.

**III.2 NON-CLINICAL ASPECTS**
**PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY**
The pharmacological, pharmacokinetic and toxicological properties of cytarabine are well-known.

No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for the non-submission of the environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.
III.3 CLINICAL ASPECTS

Pharmacokinetics
In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), a bioequivalence study is not requested if the test product is an aqueous intravenous solution containing the same active substance as the reference product. No bioequivalence study has been submitted with this application and none is required.

No new data have been submitted and none are required for applications of this type.

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinical efficacy
No new data have been submitted and none are required for applications of this type.

Clinical safety
Cytarabine has an acceptable adverse event profile. No new safety data were supplied or required for this generic application. Cytarabine has a well-established side-effect profile and is generally well-tolerated.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Form
The MAA form is medically satisfactory.

Clinical Conclusion
There are no objections to the approval of this product from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Cytarabine 100 mg/ml Solution for Injection or Infusion 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.

NON-CLINICAL
No non-clinical data were submitted and none are required for applications of this type.

EFFICACY
No new efficacy data were submitted and none are required for applications of this type. As the safety profile of cytarabine is well-known, no additional data were required. No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with cytarabine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk balance is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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