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Summary of Product Characteristics last updated on the eMC: 02/02/2010

SPC Cytarabine Injection Solution 20mg/ml and 100mg/ml

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Legal Categories
POM – Prescription Only Medicine

Active Ingredients/Generics
cytarabine

1. NAME OF THE MEDICINAL PRODUCT

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Cytarabine 20mg/ml.

Cytarabine 100mg/ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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1 ml of solution containing 20mg of cytarabine

1 ml of solution contains 100mg of cytarabine.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

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Solution for infusion or injection.

4. CLINICAL PARTICULARS

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4.1 Therapeutic indications

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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

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By intravenous infusion or injection, or subcutaneous injection.

Dosage recommendations may be converted from those in terms of bodyweight to those related to surface area by means of nomograms, as presented in Documenta Geigy.

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

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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

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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. 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 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 intrathecal and intravenous cytarabine at conventional doses in combination with other drugs.

The human liver apparently detoxifies a substantial fraction of an administered dose of cytarabine. Use the drug with caution and at reduced doses 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.

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4.5 Interaction with other medicinal products and other forms of interaction

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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

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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.

This product should not normally be administered to patients who are pregnant or to mothers who are breast ‑ feeding.

4.7 Effects on ability to drive and use machines

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Cytarabine has no effect on intellectual function or psychomotor performance. Nevertheless, patients receiving chemotherapy may have an impaired ability to drive or operate machinery and should be warned of the possibility and advised to avoid such tasks if so affected.

4.8 Undesirable effects

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Because Cytarabine is a bone marrow suppressant, anaemia, leucopenia, thrombocytopenia, megaloblastosis and reduced reticulocytes can be expected as a result of its administration. The severity of these reactions are dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

Most frequent adverse reactions include nausea, vomiting, diarrhoea, fever, rash, anorexia, oral and anal inflammation or ulceration, and hepatic dysfunction.

Infections and infestations: Pneumonia, sepsis, cellulitis at injection site, liver abscess.

Immune system disorders: Anaphylaxis, allergic oedema.

Metabolism and nutrition disorders: Anorexia.

Nervous system disorders: Neural toxicity, neuritis, dizziness, headache.

Eye disorders: Conjunctivitis (may occur with rash).

Cardiac disorders: Pericarditis.

Vascular disorders: Thrombophlebitis.

Respiratory, thoracic and mediastinal disorders: Shortness of breath, sore throat.

Gastrointestinal disorders: Pancreatitis, esophageal ulceration, abdominal pain, diarrhea, esophagitis, nausea/vomiting, oral and anal inflammation or ulceration.

Hepatobiliary disorders: Hepatic dysfunction, jaundice.

Skin and subcutaneous tissue disorders:Skin ulceration, alopecia, freckling, rash, pruritus, urticaria.

Renal and urinary disorders: Renal dysfunction, urinary retention.

General disorders and administration site conditions: Chest pain, fever.

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High Dose Therapy (see section 4.4)

Infections and infestations: Sepsis, liver abscess.

Nervous system disorders: cerebral and cerebellar dysfunction including personality changes, somnolence, and convulsion; peripheral motor and sensory neuropathies.

Eye disorders: Corneal toxicity.

Cardiac disorders: Cardiomyopathy with subsequent death.

Respiratory, thoracic and mediastinal disorders: Adult respiratory distress syndrome, pulmonary oedema.

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

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.

A Cytarabine syndrome has been described. It is characterised by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 – 12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are serious enough to warrant treatment, corticosteroids should be contemplated as well as continuation of therapy with Cytarabine.

Cases of pancreatitis have been observed with the induction of Cytarabine.

Cytarabine is not recommended for intrathecal use; however, the following side-effects have been reported with such use. Expected systemic reactions: bone marrow depression, nausea, vomiting. Occasionally, severe spinal cord toxicity even leading to quadriplegia and paralysis, necrotising encephalopathy, blindness and other isolated neurotoxicities have been reported.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

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5.1 Pharmacodynamic properties

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ATC Code: L01BC01

Cytarabine, a pyrimidine nucleoside analogue, is an antineoplastic agent which inhibits the synthesis of deoxyribonucleic acid. It also has antiviral and immunosuppressant properties. Detailed studies on the mechanism of cytotoxicity in vitro suggests that the primary action of Cytarabine is inhibition of deoxycytidine synthesis, although inhibition of cytidylic kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytocidal actions.

5.2 Pharmacokinetic properties

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Cytarabine is deaminated to arabinofuranosyl uracil in the liver and kidneys. After intravenous administration to humans, only 5.8% of the administered doses is excreted unaltered in urine within 12-24 hours, 90% of the dose is excreted as the deaminated product. Cytarabine appears to be metabolised rapidly, primarily by the liver and perhaps by the kidney. After single high intravenous doses, blood levels fall to unmeasurable levels within 15 minutes in most patients. Some patients have indemonstrable circulating drug as early as 5 minutes after injection.

5.3 Preclinical safety data

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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

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6.1 List of excipients

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Cytarabine 20mg/ml	Cytarabine 100mg/ml
Hydrochloric Acid	Hydrochloric Acid
Sodium Hydroxide	Sodium Hydroxide
Nitrogen	Nitrogen
Water for injections	Water for injections
Sodium Chloride	

6.2 Incompatibilities

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In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

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Cytarabine 20mg/ml	12 months
Cytarabine 100mg/ml	18 months

6.4 Special precautions for storage

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Store at 15°C - 25°C. Keep container in outer carton.

Cytarabine should not be stored at refrigerated temperatures (2-8^{o}C).

6.5 Nature and contents of container

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Polypropylene vials, closed with either a West S63/1704 Grey EPDM rubber stopper or a West 4110/40 Grey FluroTec® Plus-faced rubber stopper, and sealed with an aluminium crimp with a plastic flip-off top.

Cytarabine is supplied as vials containing 20mg/ml cytarabine in 5 ml (100mg) in packs of 5, or 25ml (500mg) as single vials.

Cytarabine is supplied as single vials containing 100mg/ml cytarabine in 10ml (1g) or 20ml (2g).

6.6 Special precautions for disposal and other handling

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Cytarabine 100mg/ml only:

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

Cytarabine 20mg/ml & 100mg/ml:

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

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 and Spills: To destroy, place in a high risk (for cytotoxics) waste disposal bag and incinerate at 1100^{o}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^{o}C.

7. MARKETING AUTHORISATION HOLDER

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Pharmacia Limited

Ramsgate Road

Sandwich, Kent

CT13 9NJ

UK

8. MARKETING AUTHORISATION NUMBER(S)

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Cytarabine 20mg/ml PL 0032/0197.

Cytarabine 100mg/ml PL 0032/0198.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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03 June 1999

10. DATE OF REVISION OF THE TEXT

Go to top of the page

January 2010

LEGAL CATEGORY

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POM

CCAB 6_1

More information about this product

- Patient Information Leaflets (PILs):
  Cytarabine Injection Solution 20mg/ml and 100mg/ml

Link to this document from your website: http://emc.medicines.org.uk/medicine/2572/SPC/Cytarabine Injection Solution 20mg/ml and 100mg/ml/

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