SUMMARY OF PRODUCT CHARACTERISTIC (SPC)

1. NAME OF THE MEDICINAL PRODUCT

BIOBIN
Cytarabine Injection BP 100mg/1ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Cytarabine BP	100 mg
Water for Injection BP	q.s.

For full list excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection

A clear colourless solution filled in an amber glass vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cytarabine is useful in various neoplastic disorders including acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), acute nonlymphocytic leukemia (ANLL), chronic myloid leukemia, acute promyelocytic leukemia, meningial neoplasms and carcinomatous megningitis. Cytarabine may be effective in the treatment of Non-Hodgkin's Lymphoma, malignant pleural effusions multiple myeloma, myelodysplatic syndrome and Leucoencephalopathy. Other disease state in which Cytarabine has been used include herpes virus infections and psorials.

4.2 Posology and method of administration

The correct dosage of cytarabine may vary from protocol to protocol, and may depend upon the clinical and hematological responses and tolerance of the patient.

For the treatment of AML including acute promyelocytic leukemia, intravenous (i.v.) dosage for adults and children is 100 to 200 mg/m^2/day by continuous i.v. infusion for 7 days. For intensification, 1 up to 3g/m^2 i.v. over one hour repeated every 12 hours for 8-12 doses total.

The same dose for intensification can also be used to treat refractory leukemia.

For treatment of ALL, in adults and children, in the intensification phase or for treatment of refractory leukemia, 1 up to 3g/m^2 i.v. over one hour repeated every 12 hours for 8-12 doses total.

Commonly used regimens for ANLL include the "7 + 3 regimen" and "DAT protocols". The "7+ 3 regimen" consists of cytarabine 100 mg/m^2/day by continuous infusion on days 1 through 7 (plus daunorubicin 45 mg/m^2 i.v. push on days 1 through 3). The DAT regimen consists of cytarabine 25 mg/m^2 i.v. bolus followed by 200 mg/m^2/day by continuous infusion on days 1 through 5 plus daunorubicin 60 mg/m^2 i.v. push on days 1 through 3, plus thioguanine 100 mg/m^2 orally every 12 hours on days 1 through 5. When used in combination with other cytotoxic agents, cytarabine 25 mg/m^2 as an intravenous push, and 100 or 200 mg/m^2 as a continuous i.v. infusion have been used in the treatment of ANLL.

4.3 Contraindications

One should not be treated with this medicine if one has had an allergic reaction or hypersensitivity to cytarabine.

4.4 Special warnings and precautions for use

Cytarabine therapy should not be initiated in patients who have severe bone marrow depression. Intramuscular injections should not be administered to patients receiving cytarabine as it may result bleeding, bruising, or haematomas due to thrombocytopenia secondary to Cytarabine-induced bone marrow depression. The drug should be used with caution in patients with tumour cell infiltration the bone marrow.

Cytarabine is teratogenic in some animal species. The clinical effect of chemotherapy on the fetus is highly unpredictable. It should not use during the first trimester of pregnancy. Deformities of the head and limbs are most common. One should not breast feed while getting this medicine as it is uncertain whether Cytarabine is distributed into breast milk. Also it advisable not to get pregnant while either of the sexual partner receiving cytarabine. An effective method of birth control should be used white being treated with this medicine.

Cytarabine is a known cerebellar and cerebral toxin when given in doses over 1 g/m^2. Patients with underlying central nervous system disease may be more sensitive to the effects of high dose Cytarabine. Cytarabine should be discontinued immediately with the onset of nystagmus or ataxia.

Intrathecal administration of cytarabine can cause nausea, vomiting transient headaches and fever. These effects usually disappear with continued therapy. The medicine may make patients mouth sore an irritated. It may be easier to get infections while getting this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

One should not take aspirin or any product that has aspirin in it (such as some cold medicines) unless previously discussed with the doctor. Alcohol should be avoided. Other drugs which can interact with cytarabine include digoxin, dipyridamole and methotrexate.

One should talk to his doctor before getting any vaccines. Live virus vaccines should be administered only when clearly needed during therapy with antineoplastic agents due to the potentiation of virus replication, adverse reactions to the virus and the immunocompromised status of the patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

Cytarabine is teratogenic in some animal species. It should not be used in pregnant women (especially during the first trimester) or in those who may become pregnant, unless the possible benefits outweigh the potential risks. Women who are, or who may become, pregnant during treatment with cytarabine should be informed of the risks.

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

Breast-Feeding

It is not known if cytarabine or its metabolite is distributed into breast milk, and it should not be used in mothers who are breastfeeding.

Fertility

Fertility studies to assess the reproductive toxicity of cytarabine have not been conducted. Gonadal suppression, resulting in amenorrhea or azoospermia, may occur in patients taking cytarabine therapy, especially in combination with alkylating agents. In general, these effects appear to be related to dose and length of therapy and may be irreversible. 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

No documented effect on ability to drive or operate machinery.

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 primary toxicities of cytarabine are myelosuppression, nausea, vomiting, and gastrointesinal mucositis. Children receiving standard doses of cytarabine have also been reported to have a syndrome characterizes by fever, myalgia, bone pain, and occasionally by chest pain, maculopapular rash, and conjunctivitis.

Hematological toxicity: The major toxic effect of cytarabine is myelosuppression with megaloblastic changes in erythropoiesis of the bone marrow and reticulocytopenia in the peripheral blood. Patients develop leucopenia, neutrapenia and thrornbocytopenia roughly by 7th day with resolution by 21st to 28th day. Cardiopulmonary complications of cytarabine therapy are uncommon and isolated cardiac toxicity has rarely been reported. Supraventricular and ventricular arrhythmias have been described and there is one reported case of recurrent congestive heart failure following cytarabine therapy. The "cytosine arabinoside syndrome" is characterized by high fever, malaise, joint pain and chest pain first described in children

receiving cytarabine as maintenance therapy for acute leukemia. These patients had abrupt onset of symptoms within 12 hours after initiation of therapy and the symptoms resolved within 24 hours after cessation of the drug; the aetiologyforthe chest pain is unexplained.

Respiratory toxicity: Non-cardiogenic pulmonary edema has been noted in some cases to occur within 3 days after cytarabine therapy for leukemia., however, there may have been an association with streptococcal wound infection or septicemia in these patient. In some of these cases, there has been prompt improvement with steoid therapy supporting an inflammatory effect of cytarabine.

Isolated cases of pericarditis associated with high dose cytarabine without the simultaneous occurrence of pleuritis or pulmonary failure are also reported. It is suspected that pericarditis could have been immunemediated, and indeed hypersensitivity reactions have been reported with cytarabine. Nonhematologic toxicity of cytarabine is likely related to the "Capillary leak syndrome" primarily involving the lungs. The overall incidence of ARDS (Adult respiratory distress syndrome) associated with cytarabine has been estimated to be 16%.

Central toxicity: High dose cytarabine regimens have also been associated with neurotoxicity characterized by cerebellar dysfunction. This neurotoxicity appears to be dose related, with increasing symptoms in patients receiving total doses of cytarabine mg/m^2. Severe cerebellar toxicity is seen with high dose re 48 g/m^2), Patients older than 50 years and those with renal insufficiency are at greater risk for the development of neurotoxicity. Dosage reduction should be considered in these patients. Neurotoxicity can be reduced by dose modification in patients with renal insufficiency, and a oncedaily rather than twice-daiiy administration schedule. A second course of high-dose cytarabine appears to be safe if severe cerebellar toxicity was not observed with initial course. Sensory peripheral neuropathy following cytarabine therapy has been reported in two patients with AML.

Dermatologic and occular toxicity: Cutaneous changes limited the hands have been described in patients receiving cancer chemotherapy with regimens involving cytarabine. Rash is a frequent adverse effect of cytarabine.

Hepatotoxicity: Although infrequent, elevations in serum bilirubi transaminases and alkaline phosphate have been reported to have occurred in patients receiving cytarabine. Pancreatitis has also occurred at occasions.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org'

4.9 Overdose

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

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

Cytarabine may be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pyrimidine analogues, ATC code: L01BC01

Cytarabine is a synthetic antineoplastic agent. The exact mechanism of action is unknown. It is felt that the drug is an antimetabolite, interfering with the synthesis of DNA. The inhibition of the conversion of cytidine to deoxycytidine is the presumed primary site of action. Cytarabine may also be incorporated into DNA and RNA as in vitro chromosome breaks have been associated with the drug and the clinical effects are limited to tissues with a high rate of cellular proliferation. Alternatively, cytarabine may have a differentiating role rather than an antimitotic effect as the mechanism of action. Cytarabine reportedly also has immunosuppressive activity.

Two important properties of cytarabine include: i) a relatively unique synergistic effect with other classes of drugs including alkylating agents, thiopurines, and anthracycline antibiotics, and ii) clinical effectiveness that is significantly affected by the schedule of administration. High-dose cytarabine is effective for refractory leukemiaand the addition of anthracyclines may enhance this effect.

5.2 Pharmacokinetic properties

Following intravenous administration, cytarabine is widely distributed to areas including the CNS and tears. Cytarabine is not administered orally due to poor absorption across the GI tract. It is rapidly degraded by cytidine deaminase. Subcutaneous (s.c.) or intramuscular (i.m.) administration results in lower peak plasma levels than does i.v. administration. Cytarabine distributes rapidly throughout the body tissues, and cerebrospinal fluid (CSF) concentrations are roughly 40-60% of plasma concentrations. In the CSF the half-life is longer (2-11 hours) because CSF contains no cytidine deaminase. Cytarabine achieves significant concentrations in tears, enough to cause chemical conjunctivitis. Using continuous infusion rates, steady-state plasma concentrations of the drug can be obtained in 8-24 hours.

The drug undergoes metabolism by cytidine deaminase in the liver as well as the kidneys, GI mucosa, and granulocytes. The degradation pathway can be saturated at higher doses, shunting more drug down the activation pathway than would happen with lower doses. Excretion of cytarabine is biphasic, with an initial phase half-life equal to 8 minutes and terminal phase half-life equal to 1-3 hours. The majority of a cytarabine dose is excreted via the urine in the form of metabolites, 90% of a dose is eliminated in the urine within 24 hours.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Sodium Hydroxide (pH Adustment)
- Water for Injection

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. 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.

6.3 Shelf life

30 Months

6.4 Special precautions for storage

Store at a temperature not exceeding 25˚C. Protect from light.

6.5 Nature and contents of container

Single vial contains 100mg/1ml

6.6 Special precautions for disposal and other handling

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

7.0 Marketing Authorization Holder and Manufacturing Site Addresses

Marketing Authorization holder
Name : Zydus Healthcare Limited
Address : Ackruti Star, Unit No.: 103, MIDC, Andheri (E), Mumbai – 400 093, India

Manufacturing Site Address:
Name : Khandelwal Laboratories Pvt Ltd
Address : B-1, Wagle Industrial Estate, Thane-400604, India

8.0 MARKETING AUTHORIZATION NUMBER
Registration no.2586

9.0 DATE OF REVISION OF THE TEXT
19/02/2026