

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. Name of the finished pharmaceutical product

CYBIN-PF (Cytarabine 100 mg/ ml injection)

2. Qualitative and quantitative composition

Each ml contains 100 mg cytarabine .

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Liquid injection

A clear colorless solution

4. Clinical particulars

4.1 Therapeutic indications

Cytarabine may be used alone or in combination with other antineoplastic agents. It is indicated alone or in combination for induction of remission and/or maintenance in patients with acute myeloid leukaemia, acute non lymphoblastic leukaemias, acute lymphoblastic leukaemias, acute lymphocytic leukaemia, erythroleukaemia, blast crises of chronic myeloid leukaemia, diffuse histiocytic lymphomas (non-Hodgkin's lymphomas of high malignancy), meningeal leukaemia and meningeal neoplasms. Clinicians should refer to the current literature on combination therapy before initiating treatment.

4.2 Posology and method of administration

Posology

Cytarabine Injection can be diluted with Sterile Water for Injections BP, Glucose Intravenous Infusion BP or Sodium Chloride Intravenous Infusion BP. Prepared infusions, in the recommended diluents, should be used immediately.

Alternatively, the diluted infusion fluids may be stored at 2-8°C, protected from light, but portions remaining unused after 24 hours must be discarded.

Remission induction: Adults

Continuous dosing: the usual dose in leukaemia is 2 mg/kg by rapid intravenous injection daily for ten days. If after ten days neither therapeutic response nor toxicity has been observed, the dose may be increased to 4 mg/kg until a therapeutic response or toxicity is evident. Daily blood counts should be taken. Almost all patients can be carried to toxicity with these doses.

Alternatively, 0.5 to 1 mg/kg may be infused daily in 1-24 hours for ten days, and then at a rate of 2 mg/kg/day until toxicity is observed. Continue to toxicity or until remission occurs. Results from one hour infusions have been satisfactory in the majority of patients.

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

Evidence of bone marrow improvement has been reported to occur 7-64 days after the beginning of therapy.

In general, if a patient shows neither remission nor toxicity after a trial period, then cautiously administered higher doses can be administered. Generally patients tolerate higher doses given by rapid intravenous injection rather than slow infusion.

As a single agent for induction of remissions in patients with acute leukaemia, cytarabine has been given in doses of 200 mg/m² by continuous intravenous infusion for five days at approximately 2 week intervals.

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

Leukemic meningitis: Therapy for established meningitis employs a wide variety of dose regimens but a recommended total daily dose not exceeding 100 mg, alternating with methotrexate is recommended.

Myelosuppression, anaemia and thrombocytopenia occur almost to all patients given daily infusions or injections. Myelosuppression is biphasic and nadirs at 7-9 and 15-24 days. Evidence of bone marrow improvement may be expected 7-64 (mean 28) days after the beginning of treatment.

Paediatric population: Children appear to tolerate higher doses of cytarabine than adults, and where the range of doses is given, children should receive the higher dose.

Elderly: No data is available to suggest that a change in dose is necessary in the elderly. However, the elderly patient is more susceptible to toxic reactions and therefore particular attention should be paid to drug induced leukopenia, thrombocytopenia and anaemia.

Method of administration

Cytarabine 100 mg/ml injection is a ready to use injection and can be administered by the intravenous and subcutaneous routes.

4.3 Contraindications

Hypersensitivity to cytarabine or to any of the excipients used in the formulation.

Anaemia, leukopenia and thrombocytopenia of non-malignant aetiology (e.g. Bone marrow

aplasia), unless the benefits outweigh the risk. Degenerative and toxic encephalopathies, especially after the use of methotrexate or treatment with ionizing radiation.

During pregnancy, cytarabine should only be administered on strict indication, where the benefits of the drug to the mother should be weighed against possible hazards to the foetus.

4.4 Special warnings and precautions for use

Cytarabine is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving the drug should be kept under close medical supervision. Leucocyte and platelet counts should be performed frequently and daily during induction. 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).

One case of anaphylaxis that resulted in cardiopulmonary arrest and necessitated resuscitation has been reported. This occurred immediately after intravenous cytarabine was administered.

Severe and at times fatal central nervous system (CNS), gastrointestinal (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 gastrointestinal ulceration including pneumatises cysteroideis intestinalis, leading to peritonitis; sepsis and liver abscess; and pulmonary oedema.

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

Rarely, neurological effects such as severe spinal cord toxicity even leading to necrotizing encephalopathy, quadriplegia and paralysis and blindness have been reported with cytosine arabinoside and have been predominantly associated with intrathecal administration. Isolated cases have also been reported with high intravenous doses during combination chemotherapeutic regimens.

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.

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

Cytarabine should only be used under the constant supervision by physicians experienced in therapy with cytotoxic agents. Hyperuricemia secondary to rapid lysis of neoplastic cells may occur in patients receiving cytarabine; serum uric acid concentrations should be monitored. The physician should be prepared to use such supportive and pharmacological measures as may be necessary to control this problem.

Periodic determinations of renal and hepatic functions and bone marrow should also be performed and the drug should be used with caution in patients with impaired hepatic function.

However, dosage reduction does not appear to be necessary in patients with impaired renal function. The human liver apparently detoxifies a substantial fraction of the administered dose. The drug should be used with caution and at a reduced dose when liver function is poor. Frequent platelet and leucocyte counts are mandatory.

Therapy should be suspended or modified when drug-induced bone marrow depression results in a platelet count of less than 50,000 or a polymorph nuclear count of under 1000 per mm³. Counts may continue to fall after the therapy has been discontinued and may reach lowest values after five to seven days. Therapy may be restarted when the bone marrow appears to be recovering on successive bone marrow studies. Therapy should not wait until the normal blood values are obtained to be re-initiated. If treatment is not resumed before blood values return to normal, the disease can get out of control.

When intravenous doses are given quickly, patients may become nauseated and may vomit for several hours afterwards. The problem tends to be less severe when 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 non-operative medical management.

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

Immunosuppressant effects/Increased susceptibility to infections

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

High dose therapy

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 adjustments may be needed to avoid irreversible neurologic disorders.

Severe and sometimes fatal pulmonary toxicity, adult respiratory distress syndrome, and pulmonary oedema have occurred following high dose schedules with cytarabine therapy. Cases of cardiomyopathy with subsequent death have been reported following experimental high dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation.

Paediatric population

The safety of the drug has not been established in infants.

Excipient information

Cytarabine 100 mg/ml Injection contains less than 1 mmol sodium (23 mg) in each vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other FPP's and other forms of interaction

Cardiac glycosides

GI absorption of oral digoxin tablets may be substantially reduced in patients receiving combination chemotherapy regimens (including regimens containing cytarabine), possibly as a result of temporary damage to intestinal mucosa caused by the cytotoxic agents. Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyl digoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without cytarabine or procarbazine. Limited data suggest that the extent of GI absorption of digitoxin is not substantially affected by concomitant administration of combination chemotherapy regimens known to decrease absorption of digoxin. 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 utilization of digitoxin for such patients may be considered as an alternative.

Anti-infective agents

One *in vitro* study indicates that cytarabine may antagonise the activity of gentamicin against *klebsiella pneumoniae*. In patients on cytarabine being treated with gentamicin for a *k.pneumoniae* infection, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

5-fluorocytosine:

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

Immunosuppressive agents

Due to the immunosuppressive action of cytarabine, viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body, may be associated with the use of cytarabine alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

4.6 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 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 gastrointestinal undesirable effects. Cytarabine is toxic to the bone marrow, and causes haematological undesirable effects.

Infections and infestations

Uncommon: Sepsis (immunosuppression)

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon: Lentigo

Blood and lymphatic system disorders:

Common: Anaemia, megaloblastosis, leukopenia, thrombocytopenia

Not known: Reticulocytopenia

These appear to be more evident after high doses and continuous infusions; the severity depends on the dose of the drug and schedule of administration.

Gastrointestinal disorders

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

Uncommon: Oesophagitis, oesophageal ulceration, pneumatosis cystoides intestinalis, necrotising colitis, peritonitis

Not known: Gastrointestinal haemorrhage, pancreatitis

Nausea and vomiting occur and are generally more frequent following rapid iv administration than with continuous IV infusion of the drug.

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

Not known: Rash, freckling, skin bleeding

Renal and urinary disorders

Common: renal impairment, urinary retention

Not known: Renal dysfunction

General disorders and administration site conditions

Common: Fever, thrombophlebitis at the site of injection

Uncommon: Cellulitis at the injection site

Not known: Chest pain, irritation or sepsis at the injection site, mucosal bleeding

Cardiac disorders

Uncommon: Pericarditis

Very rare: Arrhythmia

Not known: Sinus bradycardia

Hepatobiliary disorders

Common: Reversible effects on the liver with increased enzyme levels

Not known: Hepatic dysfunction and jaundice

Metabolism and nutrition disorders

Common: Anorexia, hyperuricemia

One case of anaphylaxis that resulted in cardiopulmonary arrest and necessitated resuscitation has been reported (See Special warnings and precautions for use).

Nervous system disorders

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

Uncommon: Headache, peripheral neuropathy, paraplegia at intrathecal administration

Not known: Dizziness, neuritis or neural toxicity and pain, neurotoxicity rash

Eye disorders

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

Not known: Conjunctivitis

Respiratory, thoracic and mediastinal disorders

Uncommon: Pneumonia, dyspnoea, sore throat.

Musculoskeletal and connective tissue disorders

Uncommon: Myalgia, joint pain.

A cytarabine syndrome (immunoallergic effect) is characterised by fever, myalgia, bone pain, occasionally chest pain, exanthema, maculopapular rash, conjunctivitis, nausea and malaise. It usually occurs 6-12 hours after 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. If treatment is effective, therapy with cytarabine may be continued.

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

Blood and lymphatic system disorders

Hematological toxicity has been 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.- is combined with another CNS toxic treatment such as radiation therapy or high dose of a cytotoxic agent.

Eye disorders

Reversible corneal lesion and haemorrhagic conjunctivitis have been described. These phenomena can be prevented or decreased by installation of 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. Pancreatitis has also been observed after high-dose therapy.

Hepatobiliary disorders

Liver abscesses, hepatomegaly and Budd-Chiari-syndrome (hepatic venous thrombosis) 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.

Reproductive system and breast disorders

Amenorrhoea and azoospermia

Others

Following cytarabine therapy, cardiomyopathy and rhabdomyolysis have been reported.

The gastrointestinal undesirable effects are reduced if cytarabine is administered as infusion. Local glucocorticoids are recommended as prophylaxis of haemorrhagic conjunctivitis. One case of anaphylaxis that resulted in cardiopulmonary arrest and necessitated resuscitation has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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/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: pyrimidine analogues, ATC code: L01BC01

Mechanism of action

Cytarabine (ARA-C) is metabolised *in vivo* to ARA-CTP phosphorylated compound. This competitively inhibits DNA polymerase and may also inhibit certain acid kinase enzymes.

Primarily the drug acts as a false nucleoside and competes for enzymes involved in the conversion of cytidine nucleotide to deoxycytidine nucleotide and also incorporation into the DNA.

Cytarabine has no effect on non-proliferating cells nor on proliferating cells unless in the S phase. It is a cell cycle specific antineoplastic drug

5.2 Pharmacokinetic properties

Absorption

Oral administration is ineffective due to rapid deamination in the gut. Cytidine deaminase is concentrated in the liver and intravenous doses show biphasic elimination with half-lives of approximately 10 minutes and 1-3 hours.

Elimination

After 24 hours 80% of a dose has been eliminated either as the inactive metabolite or as the unchanged cytarabine, mostly in urine but some in bile.

Distribution

CSF levels of 50% of plasma levels are achieved with intravenous infusion. Intrathecal dosing results in slower elimination ($T_{1/2}$ 2-11 hours).

Cytarabine is rapidly and widely distributed into tissues, crosses the blood brain barrier and also the placenta.

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

Water for Injections

Sodium Hydroxide

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

24 months

6.4 Special precautions for storage

Store below 25°C. Protected from light.

6.5 Nature and contents of container

2 ml flint tubular glass vial closed with 13 mm rubber plug and sealed with 13 mm flip off aluminium seal. Such one vial is packed in a carton along with pack insert.

6.6 Special precautions for disposal

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

Use in the paediatric population

No special requirements

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

7 Marketing authorization holder

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8 MARKETIBG AUTHORIZATION NUMBER

07481/07819/NMR/2019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

31/05/2022

10 DATE OF REVISION OF THE TEXT

18/07/2023