

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCTS

ARA-cell® 5 g concentrate for solution for intravenous infusion

Active substance: cytarabine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial with 50 ml concentrate for solution for infusion contains 5,000 mg cytarabine

Excipient with known effect

1 vial with 50 ml concentrate for solution for infusion contains 11.15 mmol (256.5 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, colourless to yellowish solution free of particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARA-cell® 5 g is used in combination with other cytostatic agents in high-dose therapy for:

- refractory non-Hodgkin's lymphoma
- refractory acute non-lymphocytic leukaemia
- refractory acute lymphoblastic leukaemia
- recurrent cases of acute leukaemia
- types of leukaemia with special risk:
 - secondary leukaemia following previous chemotherapy and/or radiation treatment
 - manifest leukaemia following transformation of pre-leukaemia
- consolidation of the remission of acute non-lymphocytic leukaemia in patients under 60 years of age.

4.2 Posology and method of administration

ARA-cell® 5 g is applied in combination with other cytostatic substances during complex treatment protocols in high-dose treatment.

High-dose treatments are usually carried out with 1 to 3 g cytarabine/m² body surface as intravenous infusion over 1 to 3 hours at 12-hour intervals for 4 to 6 days.

The exact dosages can be obtained from treatment protocols in specialist literature.

Since ARA-cell® 5 g is a hypertonic solution, ARA-cell® 5 g concentrate for solution for intravenous infusion must therefore not be administered intrathecally and should not be administered undiluted.

The increased risk of complications pertaining to the central nervous system should be observed when determining dosages for high-dose treatment.

Cytarabine is haemodialysable. ARA-cell® should therefore not be administered to dialysis patients immediately before or during dialysis.

The duration of administration is determined by the treating physician in dependence of the diagnosis.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Leuko-, thrombo-, and erythrocytopenia of non-malignant aetiology also represent a contraindication.

In patients over 60 years of age, high-dose treatment with cytarabine should only be administered after very careful assessment of the risks.

Cytarabine should not be administered during pregnancy. Breast-feeding should be stopped if treatment becomes necessary during lactation (see section 4.6).

Degenerative and toxic encephalopathies, especially after the use of methotrexate or treatment with ionizing radiation.

4.4 Special warnings and precautions for use

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

ARA-cell® 5 g must not be administered intrathecally and should not be administered undiluted (hypertonic solution!).

Cytarabine is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression.

For induction and consolidation in acute leukaemia, treatment with ARA-cell® should be performed only on an inpatient basis under the supervision of experienced oncologists and requires careful monitoring. Regular blood count monitoring is required, as well as monitoring of liver and kidney function and serum uric acid levels. In patients with high blast counts or extensive tumour masses (non-Hodgkin's lymphomas), preventive treatment against hyperuricaemia is recommended. Supportive therapeutic measures should be available.

Anaphylaxis

Treatment with cytarabine may be associated with anaphylactic reactions. One case of anaphylactic shock with acute cardiopulmonary failure and the need for resuscitation has been reported in the literature. This event occurred immediately after IV administration of cytarabine.

Tumour lysis syndrome

Like other cytostatic drugs, cytarabine may produce secondary hyperuricaemia following rapid lysis of neoplastic cells. Therefore, uric acid levels in the blood should be monitored at regular intervals, taking appropriate action if necessary.

Liver and kidney function

In patients with pre-existing impairment of liver or kidney function, the risk of CNS toxicity may increase, especially at higher dosages. These patients should be given cytarabine only with caution, adjusting the dosage as necessary. Periodic checks of bone marrow, liver and kidney functions should be performed in patients receiving cytarabine.

High-dose therapy

High-dose therapy with 2-3 g/m² cytarabine may be associated with serious, sometimes fatal CNS, gastrointestinal and pulmonary toxicity. The following reactions may occur: reversible corneal toxicity and haemorrhagic conjunctivitis; usually reversible cerebral and cerebellar dysfunction including personality changes, somnolence, convulsions and coma, affected alertness, dysarthria, ataxia, tremor, nystagmus, headache, confusion, dizziness, etc. appear in 8-37% of treated patients. Peripheral motor and sensory neuropathies have also been reported with high dose therapy. 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 of corticosteroid eye drops.

severe gastrointestinal ulcerations including Intestinal perforation, pneumatosis cystoides intestinalis, which may lead to peritonitis, sepsis and liver abscess, intestinal necrosis with ileus, necrotising colitis, liver damage with hyperbilirubinaemia, hepatomegaly, Budd-Chiari-syndrome (hepatic venous thrombosis) and pancreatitis.

The pulmonary toxicity includes the following reactions in particular: pulmonary oedema and acute respiratory distress syndrome (ARDS). 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.

In high-dose treatments, ongoing monitoring of CNS and lung function should be performed by doctors with proven experience of this treatment. To avoid ophthalmological complications, regular rinsing of the eyes is required in high-dose therapy.

Patients may very rarely experience severe exanthema with 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.

Following administration of high-dose cytarabine in combination with daunorubicin and asparaginase, adult patients with acute myeloid leukaemia rarely experienced peripheral motor and sensory neuropathies. Close monitoring and dose adjustment as necessary are recommended to prevent irreversible neurological injury.

Experimental high-dose therapy with cytarabine and cyclophosphamide for preparation for bone-marrow transplantation has been associated with cases of cardiomyopathy, some with a fatal outcome.

In high-dose treatment, profound Pancytopenia seen which may last 15-25 days along with more severe bone marrow aplasia than that observed at conventional doses.

In the event of severe gastrointestinal reactions, antiemetic measures and supportive therapeutic measures are indicated.

Due to the marked suppression of bone marrow function, patients receiving induction therapy or consolidation therapy should be placed in sterile isolation.

During therapy with ARA-cell[®], no vaccinations with live pathogens should be given.

As with treatment with other antitumour agents, there is a risk of bleeding complications and dangerous infections during treatment with ARA-cell[®], due to 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).

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.

If signs of CNS toxicity occur, or if there are any signs of allergy development, a special risk assessment is recommended.

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

Cytarabine is a teratogenic and mutagenic substance.

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.

Contact with the skin and mucous membranes (especially in the eye area) should be avoided.

Extravasation of cytarabine during intravenous administration must be avoided because of the risk of severe local tissue injury. Administration must be stopped immediately if there are any signs of extravasation.

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.

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

Combination therapy

The use of cytarabine in combination with other products may be associated with abdominal tenderness (peritonitis) and guaiac test positive colitis, with concurrent neutropenia and thrombocytopenia. Patients have responded to drug therapy.

Delayed progressive ascending paralysis resulting in death has been reported in children with acute myeloid leukaemia following concurrent intrathecal and intravenous administration of cytarabine in combination with other products.

Patients treated with cytarabine in combination with other products may develop acute pancreatitis.

Excipients:

ARA-cell® 5 g contains 11.15 mmol (256.5 mg) sodium per vial with 50 ml concentrate, equivalent to 12.83% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Myelotoxic interactions are to be expected in case of co-medication with other bone marrow toxic therapies (in particular other cytostatic agents, radiation).

Due to immunosuppressive action of cytarabine injection – 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.

In patients receiving digoxin/ β -acetyldigoxin concomitantly, digoxin levels must be monitored constantly during therapy with cytarabine. Even a single dose of cytarabine may lead to a reversible decrease in steady-state-digoxin plasma levels and to decreased renal elimination of glycosides. As this does apparently not occur with digitoxin, patients receiving a cytarabine therapy could be switched from digoxin to digitoxin.

Gentamicin-antagonism:

In vitro cytarabine seems to decrease the sensitivity of *K. pneumoniae* towards gentamicin. In case of unresponsiveness to gentamicin a replacement of the antibiotic agent might be indicated.

In isolated cases it was shown that the antimycotic activity of flucytosine can be inhibited by cytarabine.

Cytarabine may interfere with the determination of the protein content in the cerebrospinal fluid by means of turbidimetric measurement or a Folin-Ciocalteu assay.

4.6 Fertility, pregnancy and lactation

Cytarabine is presumed to cause severe damages to the unborn child if administered during pregnancy. Cytarabine must not be administered during pregnancy unless this is imperative (vital indication). In the case of treatment of a pregnant patient, medical consultation regarding the risk of foetal damage associated with treatment should take place.

Women should not become pregnant during treatment with ARA-cell®. Women have to use effective contraception during and up to 6 months after treatment.

If a pregnancy does occur during treatment, appropriate genetic counselling should be utilised.

Breast-feeding is prohibited during treatment.

Cytarabine may have a mutagenic effect which could induce chromosomal damage in the human spermatozoa.

Fertility studies to assess the reproductive toxicity of cytarabine have not been conducted. Gonadal suppression, resulting in amenorrhea or azoospermia, may occur in patient 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. It is therefore recommended that men treated with ARA-cell® do not father a child during and up to six months after the start of treatment as well as seek advice regarding semen cryopreservation before start of treatment due to possible irreversible infertility after treatment with ARA-cell®.

4.7 Effects on ability to drive and use machines

Due to its undesirable effects, (vomiting, dizziness, eye complaints), cytarabine may influence the ability to drive and use machines. 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 side effects caused by cytarabine depend on the dose, the method of administration and the duration of treatment. The most significant side effect caused by ARA-cell® is bone marrow suppression. The most common are gastro-intestinal undesirable effects.

In this section frequencies of undesirable effects are defined as follows: 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 (frequency cannot be estimated from the available data).

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

uncommon: Lentigo

Blood and lymphatic system disorders:

Common: Changes in blood count (leucopenia, thrombocytopenia, anaemia, megaloblastosis) are dose-dependent, with leucopenia usually reaching its lowest values on days 12 to 24. Reduced reticulocytes, morphologic alterations of the bone marrow. High-dose treatment is associated with considerable myelotoxicity. Haemorrhages.

The severity of these reactions is dose and schedule dependent.

Uncommon: Immunosuppression, sepsis.

Immune system disorders:

Very common: Cytarabine syndrome: characterised by fever, myalgia, bone pain, uncommonly chest pain, maculopapular rash, conjunctivitis and malaise. These symptoms usually occur 6-12 hours after application. Corticosteroids have proven to be effective in the prophylaxis of this syndrome.

Uncommon: Immediate type allergic reactions (urticaria, anaphylaxis).

Nervous system disorders:

Central nervous system disorders are predominantly observed during high-dose therapy. Toxic reactions of the central nervous system are rare in total doses less than 36 g cytarabine/m² body surface area. Disposition factors are advanced age, hepatic and renal insufficiency, previous CNS-treatment (radiation, intrathecal administration of cytostatic drugs) and alcohol abuse. Central nervous system disorders are mostly reversible.

Common: Cerebral/cerebellar dysfunction (nystagmus, dysarthria, ataxia, confusional states), headaches, impaired thought, somnolence, lethargy, coma, seizures and anorexia.

Uncommon: peripheral neuropathy

Rare: Dizziness, neuritis.

Not known: Reports on individual cases of peripheral nerve damages after high-dose cytarabine as well as cases of delayed progressive ascending paralysis.

Eye disorders:

Common: Conjunctivitis (may occur with rash), keratitis, photophobia, burning eyes, severe tearing and impaired vision; haemorrhagic conjunctivitis, ulcerative keratitis.

The complaints can be prevented or alleviated by frequent lavage of the eyes or prophylactic application of corticoidal eye drops.

Cardiac disorders:

Uncommon: Acute pericarditis

Very rare: Myocardial damage, transient cardiac arrhythmias, Arrhythmia.

Not known: sinus bradycardia

Respiratory, thoracic and mediastinal disorders

Uncommon: Pulmonary oedema due to an increase in the permeability of the alveolar capillaries, difficulty breathing, diffuse interstitial nia, Pneumonia, sore throat.

Gastrointestinal disorders

Common: Mucositis, mucosal ulceration (oral, anal), especially during high-dose treatment; severe diarrhoea with subsequent potassium and protein loss. Nausea and vomiting (especially after rapid intravenous injection), abdominal pain, diarrhoea, dysphagia, oral/anal inflammation or ulceration.

Uncommon: Intestinal necrosis, necrotising colitis. High-dose treatment uncommonly causes intestinal necrosis with ileus and peritonitis, Oesophageal ulceration, oesophagitis, pneumatosis cystoides intestinalis.

Hepatobiliary disorders:

Common: Increase in enzymes denoting cholestasis and hyperbilirubinaemia, Jaundice

Not known: Individual reports regarding the occurrence of hepatic vein thrombosis (Budd-Chiari syndrome).

Liver abscesses may occur.

In isolated cases, pancreatitis have been reported to occur with high-dose cytarabine therapy, Hepatic dysfunction.

Skin and subcutaneous tissue disorders:

Common: Maculopapular exanthema, erythroderma, erythema, alopecia, bullous dermatitis, urticaria, vasculitis.

Uncommon: cellulitis at injection site

Following the administration of high doses of cytarabine, up to 75% of patients develop generalised erythema including blistering and desquamation.

Uncommon: Burning pain in the palms and soles, Skin ulceration, pruritus.

Very rare: Neutrophilic eccrine hidradenitis.

Not known: Freckling, rash, Palmar-plantar erythrodysesthesia syndrome

Musculoskeletal and connective tissue disorders:

Uncommon: Myalgia and/or arthralgia in the neck region and in the legs.

Very rare: The occurrence of rhabdomyolysis has been described.

Renal and urinary disorders:

Common: hyperuricaemia, renal impairment, urinary retention.

Uncommon: Increase in plasma creatinine

General disorders and administration site conditions:

Common: Tissue damage at the site of injection, thrombophlebitis, fever and sore throat.

Not known: Following the administration of high-dose cytarabine, isolated cases of inadequate vasopressin incretion syndrome were observed.

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

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

4.9 Overdose

A chronic overdose can result in severe bone marrow suppression inter alia accompanied by massive haemorrhage and life-threatening infections as well as neurotoxicity.

The myelotoxicity of cytarabine is dose-limiting. During high-dose therapy using cumulative total doses of approx. 18-36 g cytarabine per treatment cycle, severe myelotoxicity including myelophthisis must be expected. This myelotoxicity is dose-dependent and depends, among others, on the patient's age, clinical condition and bone marrow reserves as well as other additional myelotoxic treatment. The full clinical picture appears 1 to 2 weeks after administration.

Haematological parameters must be checked frequently over an extended period of time, even in the case of a suspected overdose. As effective antidotes are not available, the utmost caution is mandatory for each application.

In case of overdose suitable supportive measures (e.g. Cessation of therapy, blood transfusions, antibiotic therapy) are indicated.

In the case of severe accidental intrathecal overdose, the CSF is to be replaced with isotonic sodium chloride solution as soon as possible.

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 can be haemodialysed. However, information regarding the efficacy in the case of overdose is not available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A cytostatic agent of the group of antimetabolites
ATC code: L01BC01

Synonyms used in literature are:

- Cytarabine (INN)
- Cytosine arabinoside
- Arabinofuranosylcytosine
- Ara-C

The chemical name for this synthetic nucleoside is 4-amino-1-pentofuranosylpyrimidin-2(1H)-one. It differs from the natural DNA component cytidine only by the steric exchange of the OH group at the C2'-atom. The chemical molecular formula is $C_9H_{13}O_5N_3$, the molar weight is 243.22. Cytarabine is instable in aqueous solution and changes into Uracil arabinoside (Ara-U) in an acid environment, whereas the pyrimidine ring opens in a strongly alkaline range. It is most stable in neutral or weakly alkaline solution.

The antineoplastic effect of cytarabine is based on selective inhibition of DNA synthesis, particularly in the S-phase. As a pyrimidine antagonist, cytarabine is converted intracellularly to arabino-sylcytosine triphosphate (Ara-CTP). Ara-CTP competitively inhibits DNA polymerase. In addition, DNA synthesis is inhibited due to incorporation of cytarabine into the DNA. The cytostatic effect of cytarabine is dose-dependent and occurs either directly in the S-phase or by protracted inhibition of DNA synthesis.

Numerous resistance mechanisms are known for cytarabine:

Inhibition of membrane transport, deficiency of phosphorylating enzymes, increased activity of inactivating enzymes, reduced affinity of DNA polymerase or increased dCTP pool. Persistently high intracellular Ara-CTP concentrations are crucial for the cytotoxic effect.

5.2 Pharmacokinteic properties

Detectable serum levels are not found following oral administration of cytarabine. Following intravenous application, cytarabine is degraded rapidly and almost completely to the inactive uracil metabolite Ara-U by the cytidine deaminase in the liver and in other tissues. Initial half-life is 1.4-7.5 minutes.

Terminal plasma half-life is approx. 10-200 minutes, on average 120 minutes. Cytarabine is eliminated slowly from the CSF, with a half-life of 2-11 hours, because of the low deaminase activity in the CNS. Following continuous intravenous infusion of conventional doses (100–200 mg cytarabine/m² body surface area), concentrations of 0.04-0.6 $\mu\text{mol/l}$ are reached. Following s.c. injection, plasma peaks are reached within 20-60 minutes, which subsequently decline biphasically. Kinetics are comparable to those following i.v. bolus injection; bioavailability is the same for both applications. High-dose treatment (≥ 1 g cytarabine/m² body surface area) is carried out to overcome cytarabine resistance, mostly as a 6-day application of 1-3 g cytarabine/m² body surface area every 12 hours as a 1 to 2 hour infusion. Cytarabine plasma levels of 10-140 $\mu\text{mol/l}$ are reached. A small amount of the cytarabine is phosphorylated intracellularly to the active metabolite Ara-CTP by kinases. Plasma protein binding of cytarabine is 2-20%.

Cytarabine passes the blood-liquor barrier. 10-40% of plasma concentrations are found in cerebrospinal fluid during continuous infusion. The elimination of cytarabine from the plasma is accompanied by its metabolism. Following conventional or high doses, only 4-10% of the applied doses are excreted renally as unchanged cytarabine, whereas 71-96% appear in the urine during the first 24 hours as Ara-U.

5.3 Preclinical safety data

a) Acute toxicity

Analyses on acute toxicity resulted in the following LD50 values:

Mouse:

Approx. 2,000 mg cytarabine/kg i.v.

>5,000 mg cytarabine/kg i.p.

1,930 mg cytarabine/kg p.o. female

3,550 mg cytarabine/kg p.o. male

Rat:

>1,000 mg cytarabine/kg i.p.

Rhesus monkey:

>2,000 mg cytarabine/kg i.v.

b) Subchronic and chronic toxicity

Tests performed on mice, rats, dogs and monkeys with regard to subchronic toxicity (from 8 days to a maximum of 4 weeks) do partly not comply with the present state of scientific knowledge. In particular, bone marrow suppression with changes in the blood count (leukopenia) was observed.

No investigations on the chronic toxicity of cytarabine are available.

c) Mutagenic and tumorigenic potential

Cytarabine is mutagenic in animal experiments. In humans, increased chromosomal damage in peripheral lymphocytes has been observed following treatment with cytarabine.

Long-term investigations on the tumorigenic potential are not available. Investigations on mice and rats carried out over six months did not provide an indication for increased tumorigenic potential.

d) Reproductive toxicity

Cytarabine showed teratogenic effects in several animal species. Anomalies involving the skeleton, eyes, brain and kidneys occurred. Data regarding humans is insufficient. The relative risk of malformation is approx. 1:8. Anomalies observed so far affected the extremities, the outer ear and the auditory canal. Exposure in the 3rd trimester of pregnancy can result in or contribute to growth retardation and pancytopenia in fetuses/neonates.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium (s)-lactate solution 50%

Water for injections

6.2 Incompatibilities

There is in vitro incompatibility with fluorouracil, gentamicin, penicillin G, oxacillin, heparin (not with ready-to-use solutions), insulin, methylprednisolone and methotrexate.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Any portion of the contents remaining after use should be discarded.

Preparation

Chemical and physical in-use stability (after dilution in 0.9% sodium chloride solution or in 5% glucose solution) has been demonstrated for 10 days at room temperature (25°C) or in the refrigerator (2-8°C).

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

Additionally, when preparing the solution, the usual contact time of the disinfectant and the stopper of minimum 30 seconds prior pricking must be followed. Solutions for long term infusions are to be prepared immediately prior use.

6.4 Special precautions for storage

Store between 15°C and 25°C.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Transparent vials with rubber stopper and aluminium flip-off caps.

Original packs of 1 vial with 50 ml concentrate for solution for infusion.

6.6 Special precautions for disposal and other handling

For preparation of the solution for infusion 0.9% sodium chloride solution or 5% glucose solution can be used.

Observe the safety measures for hazardous substances during preparation and application. Observe the valid national safety measures pertaining to handling cytostatic agents when handling ARA-cell®

The solution may crystallise at temperatures below 15°C. Cloudy or precipitated solutions should be excluded from use. Use clear solutions only.

Special precautions for disposal of unused medicinal products:

Any unused medicinal product, waste material, or any materials which have come into contact with ARA-cell® should be disposed of in accordance with local requirements for cytotoxic compounds.

7. MANUFACTURER

Stadapharm GmbH
Stadastrasse 2-18
61118 Bad Vilbel
Germany

8. REGISTRATION HOLDER

MBI Pharma Ltd.
P.O.B 5061,
Kadima
Israel

9. MARKETING AUTHORISATION NUMBER

155-77-34211-00

10. LEGAL CATEGORY

Prescription only medicine

Revised in November 2021 according to MOH guidelines