1. **NAME OF THE MEDICINAL PRODUCT**

Alexan®, injection liquid 50mg/ml

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
1ml contains 50.0mg cytarabine as active ingredient.

For excipients, see 6.1.

3. **PHARMACEUTICAL FORM**
Solution for injection.
The solution is a clear and colourless solution.

4. **CLINICAL PARTICULARS**

4.1. Therapeutic indications
Cytarabine can be used as monotherapy or in combination with other chemotherapeutics in adults and children with:

- Acute myeloid leukaemia (AML)
- Acute lymphoblastic leukaemia (ALL)
- Chronic myeloid leukaemia (CML)
- Intermediate non-Hodgkin's lymphomas and high malignancy non-Hodgkin's lymphomas (such as lymphoblastic non-Hodgkin's lymphomas and Burkitt-type non-Hodgkin's lymphomas).
- IProphylaxis and treatment of leukaemia in the central nervous system: cytarabine can be administered intrathecally in combination with methotrexate and corticosteroids.

4.2. Dosage and method of administration
Cytarabine must only be administered in specialised clinics, by doctors with extensive experience of chemotherapy, and who can offer sufficient opportunities for supportive treatment.

Cytarabine is inactive orally. The dosage and administration method are dependent on the treatment schedule to be followed.

Before commencing a chemotherapy, the doctor must be aware of the professional literature in the matter, unwelcome side effects, precautionary measures, contra-indications and warnings in the context of the drugs included in the therapy programme.

Cytarabine can be administered as a single drug or in combination with other cytotoxic drugs, or occasionally corticosteroids.

It is only possible to give general recommendations, as leukaemia is often treated with combinations of cytotoxic drugs, for which a number (2–5) of drugs are used. For the various treatment schedules, refer to the professional literature.

Alexan® can be administered both intravenously (by infusion or by injection) and subcutaneously. For preparation of an infusion liquid, Alexan® can be added to 0.9% sodium chloride solution and 5% glucose solution.

Rapid intravenous infusion of cytarabine is tolerated better than continuous infusion of the same dose. This is connected to the rapid inactivity of the drug and, as a result of the rapid administration, the short exposure of normal and neoplastic cells to significant levels of the drug.

Dosage

Remission induction
Conventional doses for remission induction are 100 to 200mg of cytarabine/m^2 of body surface daily, in most cases administered as continuous intravenous infusion or rapid infusion for a period of 5 to 10 days.

Duration of treatment depends on clinical and morphological results (bone marrow). The patient may be treated either up to 7 days followed by a therapy free interval of 7–9 days till remission of the bone marrow; afterwards treatment cycles (often restricted) may be continued till remission or occurrence of toxicity or treatment may be continued till occurrence of a bone marrow hypoplasia, which has to be considered as a level of tolerance.

Before repeating treatment cycles (often restricted) a therapy free interval of at least 14 days, better till recovery of the bone marrow must be guaranteed.

Remission maintenance
The dosages for remission maintenance usually are 70 to 200mg of cytarabine/m^2 of body surface daily as rapid intravenous injection or as subcutaneous injection daily for five days at a 4–week interval or once weekly.

Therapy of non-Hodgkin's lymphomas
Therapy in adults:

Suitable polychemotherapy schedules are used for this indication, e.g. the PROMACE-CYTABOM regimen. The dosage of cytarabine is 300mg/m^2 of body surface on day 8 of the respective therapy cycle.

Therapy in children:

The usage of cytarabine in non-Hodgkin's lymphomas in children depends on the stage of disease and the histological type. It is applied within different treatment protocols at different dosages, respectively. The following protocols and dosages are a selection of combination therapies which are considered as effective according to the present scientific knowledge. Details can be found in the respective medical literature.

150mg of cytarabine/m^2 of body surface as one-hour intravenous infusion every 12 hours on days 4 and 5 of the therapy segment denominated "part A" or "part AA" in the protocol (altogether 4 intravenous infusions); in combination with other cytotoxic drugs (BFM protocols for B-cell lymphomas at stage II and III or stage IV).

75mg of cytarabine/m^2 of body surface on day 31 to 34, 38 to 41, 45 to 48, and 52 to 55 of induction therapy; in combination with other cytotoxic drugs (BFM protocol for non-B-cell lymphomas at stage I and II).

High-dose therapy
High-dose therapies are usually carried out with 1 to 3 g of cytarabine/m^2 of body surface as intravenous infusion during 1 to 3 hours at intervals of 12 hours for 4 to 6 days.

Treatment of central nervous system localisation of leukaemia

Intrathecal administration
The usual dosage varies from 5mg to 75mg per square metre of body surface area.

The administration frequency and dosage varies from regimen to regimen. The most frequently used dosage is 30mg/m^2 once every four days, until the cerebrospinal fluid no longer contains an elevated number of malignant cells.

If the solution for injection for intrathecal administration must be diluted, 0.9% sodium chloride **without** preservative must be used as diluent.

4.3. Contra-indications
Patients who have already received a drug which can induce bone marrow suppression should not be treated with Alexan®, unless the clinician deems such a treatment to be vitally important to the patient.

Hypersensitivity to cytarabine or of one of the other ingredients.

4.4. Special warnings and precautions for use
Alexan® must only be administered by specialists with experience in chemotherapy of malignant disorders.

Alexan® is a cytotoxic product. Patients treated with Alexan® must therefore be kept under strict supervision.

Rapid intravenous doses are gastro-intestinally better tolerated than slow intravenous infusions.

In view of the fact that the product is to a large extent broken down in the liver, the drug must be administered with extreme caution and in a low dosage to patients with liver function disorders.

Cytarabine must not be administered to patients with acute and/or serious infections.

Both male and female patients who are sexually mature must take contraceptive measures during and until six months after the therapy with Alexan®.

No effects have been observed as a result of exposure during handling. Slight irritation of the eye is possible. Repeated or continuous contact with the skin can lead to irritation. After accidental contact, wash the area of skin with copious amounts of water and soap.

Each treatment of a patient with acute leukaemia will unavoidably result in a more or less serious - but temporary - bone marrow depression. Control of the number of platelets and granulocytes in the blood is necessary to determine whether support treatment is necessary. The effect of the treatment is determined by measuring the number of leukaemic blast cells in the blood and bone marrow.

It is important that liver and kidney function tests are carried out regularly.

Cytarabine can lead to increased uric acid levels in the blood, as a result of a lysis of the neoplastic cells. Regular monitoring of the uric acid levels in the blood is therefore recommended. If necessary, supporting and pharmacological measures should be taken to get the hyperuricaemia under control. In the case of patients with a high number of blast cells or large tumour masses (non-Hodgkin's lymphomas) prophylaxis of hyperuricaemia is required.

In addition to the predictable haematological toxicity, in some cases serious or life-threatening side effects can occur to the CNS, the gastrointestinal tract or the lungs.

Patients with gastrointestinal ulcers, or who have recently had an operation must be kept under close observation for indications which point to haemorrhaging, and if necessary platelets must be administered by transfusion, as required.

High-dose cytarabine toxicities:
The toxicity of high dose cytarabine can be more severe than the toxicity of normal dose of cytarabine, and may include cerebellar and cerebral toxicity, conjunctivitis (make sure the patient is on steroid eye drops during therapy), corneal keratitis, exanthema, hyperbilirubinaemia, liver damage, GI perforation, pancreatitis, pulmonary oedema, pericarditis, and tamponade.

4.5. Interaction with other drugs and other forms of interaction
Combining Alexan® with other oncolytic agents, myelosuppressive drugs or radiation treatment can sometimes reduce the immunosuppressive effect of these drugs. Modification of the dosage may be necessary. Cytarabine is often administered in combination with other drugs.

The absorption of digoxin may be reduced if digoxin is combined with chemotherapeutics (including cytarabine). This is probably dependent on temporary damage to the mucosa. The plasma levels of digoxin must therefore be monitored.

An in vitro study has shown that cytarabine can counteract the effect of gentamicin against Klebsiella pneumoniae.

Alexan® must not be administered with methotrexate or 5-fluorouracil.

Combination of fluorocytosine with cytarabine can lead to a reduced effectiveness of fluorocytosine.

4.6. Pregnancy and breast feeding

Pregnancy
During pregnancy, cytarabine may only be administered on strict indication, in which context the benefits of the drug for the mother must be weighed against the possible dangers to the foetus. Animal studies have shown that cytarabine has embryotoxic and teratogenic effects (see section 5.3).

Men and women must use effective contraceptives during treatment and for six months thereafter.

Lactation
It is not known whether cytarabine is secreted in mother's milk. As many drugs are secreted in mother's milk and as cytarabine can be responsible for serious side effects in the neonate, breastfeeding should be stopped during treatment with Alexan®.

4.7. Influence on driving ability and ability to operate machinery
Cytarabine has no effect on psychomotor performance. Nevertheless, patients receiving chemotherapy have a reduced ability to drive or operate machinery, and should be warned of the risk and advised to avoid this type of activity if this occurs.

Patients who are subject to incidental occurrences of vomiting, dizziness and eye complaints are advised not to drive vehicles or operate machinery.

4.8. Side effects
Side effects of cytarabine are dose dependent. The most common are gastrointestinal side effects, and cytarabine is toxic to the bone marrow (myelosuppression) and causes haematological side effects.

Blood and lymphatic system disorders

Common:
Anaemia, megaloblastosis, leukopenia, granulocytopenia, thrombocytopenia, bleeding.

Uncommon:
Sepsis, immunosuppression.

Immune systeme disorders

Very common:
Cytarabine (Ara-C) syndrome: fever, myalgia, bone pain, incidental chest pain, exanthema, conjunctivitis and nausea may occur 6–12 hours after the start of the therapy. Corticosteroids can be used as prophylaxis and therapy. If these are effective, the therapy with cytarabine can be continued. Myelosuppression can be severe and prolonged.

Uncommon:
Allergic oedema, anaphylaxis. One case of anaphylaxis has been reported, which resulted in cardiopulmonary arrest for which resuscitation had to be applied. This occurred immediately after intravenous administration of cytarabine.

Nervous system disorders
The chance of CNS toxicity increases if cytarabine is administered intrathecally, the intrathecally cytarabine treatment is combined with other treatments which are toxic to the CNS, such as radiation, high dose therapy, or intrathecal methotrexate, or if the cytarabine treatment is intrathecally administered with short intervals or in doses above 30mg/m^2.

Common:
In the event of high dosages, cerebellar or cerebral toxicity with decreased of consciousness level, dysarthria, nystagmus, seizure (when given intrathecally), headache, dizziness, neuritis.

Uncommon:
Paraplegia in the case of intrathecal administration.

Very rare:
Necrotising leukoencephalopathy, paraplegia or quadriplegia have been reported after intrathecal treatment.

Eye disorders

Common:
Reversible haemorrhagic conjunctivitis (photophobia, stinging, visual disorders, increased lacrymation), keratitis. Locally administered glucocorticoids are

recommended as prophylaxis against haemorrhagic conjunctivitis.

Very rare:
Blindness has been reported after intrathecal treatment.

Cardiac disorders

Uncommon:
Pericarditis, chest pain.

Very rare:
Arrhythmia. Cardiomyopathy has been reported after cytarabine therapy.

Respiratory, thoracic and mediastinal disorders

Uncommon:
Pneumonia, dyspnea, sore throat, interstitial pneumonitis, syndrome of sudden respiratory distress progressing to pulmonary oedema.

Gastrointestinal disorders
The side effects to the gastrointestinal tract are reduced if cytarabine is administered as an infusion.

Common:
Mucositis, stomatitis, anorexia, dysphagia, abdominal pain, nausea, vomiting, diarrhoea, oral/anal inflammation or ulceration.

Uncommon:
Oesophagitis, oesophageal ulceration, pneumatosis, cystoides intestinalis, necrotising colitis, GI perforation, nausea, vomiting after intrathecal administration.

Hepato-biliary disorders

Common:
Reversible effects on the liver with increased enzyme values.

Uncommon:
Jaundice.

Skin and subcutaneous tissue disorders

Common:
Reversible side effects to the skin, such as erythema, bullosis, urticaria, vasculitis, alopecia.

Uncommon:
Lentigo, cellulitis at the injection site, skin ulceration, pruritis, burning pain on the palms of the hands and soles of the feet.

Very rare:
Neutrophilic eccrine hidradenitis.

Musculoskeletal, connective tissue and bone disorders

Uncommon:
Myalgia, arthralgia.

Very rare:

Rhabdomyolysis has been reported after cytarabine therapy.

Renal and urinary passage disorders

Uncommon:
Kidney function disorders, urinary retention.

General disorders and administration site disorders

Common:
Fever, thrombophlebitis at the injection site, hyperuricaemia.

Uncommon:
Fever after intrathecal administration.

4.9. Overdose
In the event of an overdose, therapy must be stopped, followed by treatment of the subsequent bone marrow depression, including total blood or platelet transfusion and antibiotics, as required.

In the event of intrathecal overdose, the cerebrospinal fluid must immediately be replaced with isotonic salt solution.

Cytarabine can be removed by means of haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. *Pharmacodynamic properties*

Pharmacotherapeutic category:
Antimetabolite (pyrimidine analogue)

ATC Code: L01BC01

Alexan® contains the active ingredient cytarabine, an antimetabolite from the series of pyrimidine antagonists.

Cytarabine is a cell-cycle-phase-specific antineoplastic agent, which can only affect cells during the S-phase of cell division. It is converted intracellularly into cytarabine-5' triphosphate (ara-CTP), which is the active metabolite. The mechanism of action is not completely understood, but it appears that ara-CTP acts primarily through inhibition of DNA polymerase. Incorporation into DNA and RNA may also contribute to cytarabine cytotoxicity. Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture.

5.2. Pharmacokinetic properties

Absorption
Cytarabine is rapidly metabolised and is orally ineffective. Less than 20% of a dose administered orally is absorbed in the gastrointestinal tract.

In the event of continuous intravenous administration, virtually constant plasma levels are achieved.

After subcutaneous administration of cytarabine, peak plasma levels are achieved approximately 20 to 60 minutes after injection which are significantly lower than after intravenous administration.

Cytarabine serum levels can vary considerably from patient to patient for an identical dose. Some studies have shown that these variations could be linked to the clinical response: high serum levels guarantee the best chance of haematological remissions.

Distribution
Cytarabine has a distribution volume of 0.7 l/kg. Cytarabine should be intrathecally administered as prophylaxis and in the treatment of CNS leukaemia, because intravenously administered cytarabine only crosses the blood-brain barrier in limited quantities. Intrathecal administration of cytarabine results in extremely low plasma levels.

Metabolism
Cytarabine is converted rapidly by deoxycitidine kinase and other nucleotidases into its active form (cytarabine-5' triphosphate) by phosphorylation in leukaemic blast cells and in healthy bone marrow. Metabolism into the inactive compound uracilarabinoside (1-beta-D-arab inofuranosyluracil) by means of cytidine deaminase activity takes place primarily in the liver, and to a lesser extent in the other tissues and blood.

It is assumed that the balance between kinase and deaminase levels can form an important factor in the determination of whether the cell is sensitive or resistant to cytarabine.

Protein binding
Binding to plasma protein is low (13.3%) with concentrations of 0.005–1mg/l.

The percentage of bound drug was independent of the concentration within the limits indicated.

Excretion
After a rapid intravenous infusion of cytarabine, biphasic elimination from the blood takes place. There is an initial distribution phase with a half life of approx. 10 minutes, followed by a secondary elimination phase with a half life of 1–3 hours.

After 24 hours, approx. 80% of the administered cytarabine is found in the urine, 90% of which is excreted as inactivated metabolite and 10% as unchanged cytarabine.

Due to the low cytarabine deaminase activity in the cerebrospinal fluid, cytarabine has an elimination half life in the CNS of 3–3.5 hours.

5.3. Data from pre-clinical safety studies
Studies have reported that cytarabine is genotoxic (in vivo and in vitro) as well as embryotoxic and teratogenic, if exposed to pregnant mammals during the organogenesis in clinically relevant dosage regimen.

It is also reported that cytarabine causes damage to the developing brain if administered to newborn mammals (period equivalent to third trimester in humans) and increases the frequency of abnormal spermatozoa in vivo in mice.

It has been shown that cytarabine is carcinogenic in animals. The possibility of a comparable effect must be taken into account when determining the long-term strategy for the patient.

6. PHARMACEUTICAL PARTICULARS

6.1. List of additives
Sodium lactate
Lactic acid
Water for injections

6.2. Cases of incompatibility
Cytarabine is physically incompatible with heparin, insulin, methotrexate, 5-fluorouracil, nafcillin, oxacillin, benzylpenicillin and methylprednisolone sodium succinate.

6.3. Storage life
3 years.

Storage life after reconstitution
Chemical and physical stability after dilution with 0.9% (m/v) sodium chloride solution and 5% (m/v) glucose solution has been demonstrated for 4 days at 2–8°C and for 24 hours when stored at a temperature below 25°C.

In the event that reconstitution/ mixture does not take place under aseptic conditions, the storage life of the reconstituted (diluted) product must be limited from a microbiological point of view must be limited to 24 hours at 2–8°C or a maximum of 12 hours at temperatures below 25°C.

6.4. Special precautions for storage
Store in the original packaging. Keep the drug out of reach of children.
Do not store above 25°C.

6.5. Nature and contents of the container
1 vial containing 500mg/10ml of cytarabine.
1 vial containing 1000mg/20ml of cytarabine.
1 vial containing 2000mg/40ml of cytarabine.

6.6. Instructions for use and handling
Alexan® must be diluted for infusion with 0.9% sodium chloride solution or 5% glucose solution.

Compatibility with 0.9% sodium chloride solution and 5% glucose solution has been studied in concentrations of 0.2–3.2mg/ml in PVC infusion bags, PE infusion vials and perfusion syringes.

For intrathecal administration, 0.9% sodium chloride without preservative must be used as diluent.

If cytarabine comes into contact with the skin, the exposed area must be rinsed with copious amounts of water, and then washed thoroughly with water and soap. If the solution comes in contact with the eyes, rinse the eyes extremely carefully with copious amounts of water, then contact an eye specialist immediately.

Pregnant employees should be excluded from working with this drug.

After use, bottles and injection materials, including gloves, must be destroyed in accordance with the rules for cytotoxic drugs.

Spilled or leaked product can be inactivated with 5% sodium hypochlorite solution. All cleaning materials must be cleared away as indicated above.

7. MANUFACTURER
EBEWE Pharma Ges.m.b.H. Nfg.KG
A–4866 Unterach, AUSTRIA

8. DATE OF REVISION OF THE SUMMARY
Most recent revision of the summary: July 2004