SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alexan

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Alexan 50 mg/ml – vial:
Each ml contains 50 mg of cytarabine in stabilized aqueous solution.

Vial of 10 ml contains 500 mg cytarabine.
Vial of 20 ml contains 1,000 mg cytarabine.
Vial of 40 ml contains 2,000 mg cytarabine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cytarabine is indicated for induction and maintenance of clinical remission in patients with acute myeloid leukemia, acute non-lymphoblastic leukemias, acute lymphoblastic leukemias, blast crises of chronic myeloid leukemia, diffuse histiocytic lymphomas (non-Hodgkin's lymphomas of high malignancy).

4.2 Posology and method of administration

Effective plasma levels are assumed to range between 0.01 and 0.15 g/ml. The dose must be determined exactly for each individual patient, ideally in relation to the body surface area (BSA). Unless otherwise specified for certain combinations, cytarabine should be administered in the below indicated dosages:

Standard dosage
Induction therapy in patients with acute leukaemia
Intravenous injection 100-200 mg/m^2 of body surface area, daily.
Intravenous infusion of 100 mg/m^2 of body surface area, daily.
The above doses are suggested as a guideline and may be exceeded during therapy.
The duration of therapy is dependent on the clinical and morphological findings (bone marrow).
The patient may receive a treatment course of up to 7 days, which is followed by a treatment-free interval of 7-9 days to allow for sufficient recovery of the bone marrow; consolidation courses (often shorter) may subsequently be undertaken until remission or toxicity occurs.

Alternatively, therapy may be continued until bone marrow hypoplasia occurs, which is to be regarded as the tolerance limit.
Each consecutive treatment course (often shorter) must be preceded by a therapy-free interval of at least 14 days or until the bone marrow has sufficiently recovered.

Maintenance therapy in patients with leukaemia
75-100 mg/m^2 of body surface area daily are administered once a month on five consecutive days, or once a week.

CNS involvement
Doses range from 5 mg/m^2 to 75 mg/m^2 of body surface once daily for 4 days or once every 4 days. The most common dose is 30 mg/m^2 of body surface every 4 days, until cerebrospinal fluid findings are normal, followed by one additional treatment.
The dosage schedule is usually governed by the type and severity of central nervous system manifestations and the response to previous therapy.

Lymphoma
This disease is generally treated using an appropriate combination therapy.

High-dose therapy
Unless otherwise specified, a high-dose of cytarabine is administered 3 g/m^2 I.V. every 12 hours for 4-12 doses (repeated at 2-3 week intervals).
Therapies using 4-6 doses every 2 weeks or 9 doses every 3 weeks appear equally effective and less toxic.
Total dosage and duration of therapy must be determined by the treating clinician.
Depending on the number of infusions given, the treatment course may be repeated after the bone marrow has sufficiently recovered.

Combined chemotherapy
In cases of persistent leukaemia, administer additional courses (complete or modified) of any combination, as necessary, at 2-4 week intervals.

Cytarabine Doxorubicin	100 mg/m^2/day, by continuous I.V. infusion, on days 1-10 30 mg/m^2/day, by I.V. infusion over 30 minutes, on days 1-3
Cytarabine Thioguanine Daunorubicin	100 mg/m^2/day, by I.V. infusion over 30 minutes every 12 hours, on days 1-7 100 mg/m^2/day, orally, every 12 hours, on days 1-7 60 mg/m^2/day, by I.V. infusion, on days 5-7
Cytarabine Doxorubicin Vincristine Prednisolone	100 mg/m^2/day, by continuous I.V. infusion, on days 1-7 30 mg/m^2/day, by I.V. infusion, on days 1-3 1.5 mg/m^2/day, by I.V. infusion, on days 1 and 5 40 mg/m^2/day, by I.V. infusion, every 12 hours, on days 1-5
Cytarabine Daunorubicin Thioguanine Prednisolone Vincristine	100 mg/m^2/day, by I.V. infusion, every 12 hours, on days 1-7 70 mg/m^2/day, by I.V. infusion, on days 1-3 100 mg/m^2/day, orally, every 12 hours, on days 1-7 40 mg/m^2/day, orally, on days 1-7 1 mg/m^2/day, by I.V. infusion, on days 1 and 7

Cytarabine Daunorubicin	100 mg/m^2/day, by continuous I.V. infusion, on days 1-7 45 mg/m^2/day, by I.V. push, on days 1-3

Type and duration of therapy

Standard therapy

Alexan may be administered:

- intravenously as a continuous infusion,
- intravenous injection,
- intrathecal injection,
- in exceptional cases, also as a subcutaneous injection.

Due to the short half-life of cytarabine when applied intravenously, plasma levels in most patients fall below the minimum therapeutic value in less than one hour. Therefore, it is essential to split the daily dose in two or more separate doses to be given at equal intervals. Alexan solution for infusion may be prepared using physiological sodium chloride solution or 5% glucose solution. Duration of long-term infusions reportedly is in the range of 8-12 hours and 120-168 hours. Compared to single intravenous injection, administration of the same doses as a continuous infusion results in more pronounced adverse effects on the gastrointestinal tract.

In case of administration via the intrathecal route, the recommended procedure is to extract 5-8 ml of cerebrospinal fluid, mix it with the solution for injection in the same syringe and slowly re-inject the mixture.

Systemic toxicity is not expected with this method of application.

Subcutaneous injection is only applied in exceptional cases and generally only when used in maintenance therapy.

Intracutaneous injection must be avoided due to the risk of oedemas.

High-dose therapy

Alexan is administered as an intravenous infusion for 1-3 hours.

If administered by means of a perfusor, Alexan may also be given in its undiluted form.

For preparation of a diluted solution for infusion, physiological sodium chloride solution or 5% glucose solution may be used.

All Alexan preparations are compatible with each other and may be combined to prepare an individually prescribed dose. Thus no residual amounts of the medicinal product are generated.

Note: Cytarabine has been used intrathecally with hydrocortisone sodium succinate and methotrexate, both as prophylaxis in children with newly-diagnosed acute lymphocytic leukaemia, and in the treatment of meningeal leukaemia.

Prophylactic triple therapy has been reported to prevent CNS disease, and gives overall cure and survival rates similar to those seen in patients in whom CNS radiation and intrathecal methotrexate were used as initial CNS prophylaxis. The dose of Alexan was 30 mg/m2, hydrocortisone sodium succinate 15 mg/m2 and methotrexate 15 mg/m2.

Use in 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.

Use in the elderly

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.

Use in infants
The safety of this drug for use in infants has not been established.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- This treatment must be ruled out for patients with existing bone marrow suppression.
- Severe hepatic or renal impairment, existing severe infections, gastrointestinal ulcers and recent surgery.
- Anaemia/erythrocytopenia, leukopenia and/or thrombocytopenia of non-malignant aetiology (e.g. bone marrow aplasia), unless the treating physician considers treatment with Alexan to be the most promising alternative for the patient.
- Breast-feeding (see section 4.6).
- Alexan must not be given in combination or within 4 weeks of treatment with brivudine, sorivudine and analogues. Brivudine, sorivudine and their analogues are potent inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD), which breaks down 5-FU (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Cytarabine should only be used with caution in specialised oncological institutions with facilities for regular monitoring of clinical, biochemical and haematological parameters before, during, and after administration. The usual precautions must be followed when handling the vials (safety glasses, gloves, mouth and nose protection, exhaust ventilation if possible). Particular care must be taken to ensure that facilities are available to monitor the effect on the patient and take appropriate measures if necessary.

<u>Haematological effects</u>
Cytarabine has a potent myelosuppressive effect. The treatment should be initiated carefully in patients with a history of medication-induced bone marrow suppression.
Patients who receive this medicinal product must be closely monitored. Furthermore, at the beginning of the treatment, the leukocyte and platelet counts should be determined daily. In general, the platelet and leukocyte counts should be determined as frequently as possible and regularly monitored after the end of therapy. This also applies to intrathecal use.
If a drug-induced bone marrow suppression has resulted in a platelet count <50,000 or polymorphonuclear count <1,000/mm^3, the therapy should be discontinued or modified. The number of formed elements in peripheral blood can further decrease following administration of the medicinal product has ceased, and reaches nadir after 5−7 medication-free days. If indicated, the therapy should be re-started if obvious signs of bone marrow recovery are seen (in consecutive bone marrow tests). For patients in whom the medicinal product is not administered until the “normal” peripheral blood values are achieved, monitoring is not required.

Regular bone marrow tests should be performed once peripheral blood shows no more blasts.

Facilities should be available to treat the possibly fatal complications of bone marrow suppression (infections due to granulocytopenia and other affected defence mechanisms, secondary haemorrhaging due to thrombocytopenia).

Tumour lysis syndrome
Like other cytostatics, cytarabine can cause hyperuricaemia due to rapid lysis of neoplastic cells. The physician should monitor the uric acid levels in the blood and be prepared to use supportive and pharmacological measures that may be required to control the complications that arise.
In patients with high blast counts or extensive tumour masses (non-Hodgkin's lymphoma), hyperuricaemia prophylaxis is recommended. Facilities for supportive measures should be available.

Hepatic and renal impairment are considered to be predisposing factors for the increased CNS toxicity of cytarabine.

Anaphylactic reactions occurred during cytarabine therapy. One case of anaphylaxis was reported, which lead to acute cardiopulmonary arrest, requiring resuscitation. This occurred immediately following intravenous administration of cytarabine (see section 4.8).

High-dose therapy
The risk of CNS undesirable effects is higher for patients who were previously treated for a CNS disorder with intrathecal chemotherapy or radiation therapy.

In patients with acute non-lymphatic leukaemia, peripheral motor and sensory neuropathy occurred following consolidation with high-dose cytarabine, daunorubicin and asparaginase therapy. Patients treated with high cytarabine doses should be investigated for neuropathy, as dose adjustments may be required to prevent irreversible neurological damage.

Following some experimental high-dose regimens (2–3 g/m^2) with cytarabine, severe and occasionally fatal toxicity of the central nervous system, the gastrointestinal tract and the lungs (unlike with conventional therapy regimens with cytarabine) have been reported. These reactions included reversible corneal toxicity; cerebral and cerebellar dysfunction, usually reversible; somnolence; seizures; severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis, which led to peritonitis; septicaemia and hepatic abscess; adult respiratory distress syndrome (ARDS) and pulmonary oedema (see section 4.8).

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

If the intravenous dose is administered quickly, patients are often nauseous, with vomiting occurring for several hours after administration. This problem is less pronounced if the medicinal product is infused.

Conventional dose regimen
In patients who were treated with conventional cytarabine doses in combination with other medicinal products, abdominal tenderness (peritonitis) and guaiac-positive colitis with neutropenia and thrombocytopenia were reported. These patients responded to non-surgical medical treatment.

In children with AML, delayed progressive, ascending and fatal paralysis was reported following intrathecal and intravenous administration of conventional cytarabine doses in combination with other drugs.

Hepatic and renal function:

Hepatic and renal function should be monitored during a cytarabine therapy. Special caution is required in cases of mild hepatic and renal impairment.
Periodic tests of bone marrow, hepatic and renal function should be performed on patients receiving cytarabine.

As cytarabine is predominantly metabolized in the liver, the substance may have a stronger effect in hepatic damage. An increased effect is also seen in renal impairment. In cases of renal and/or hepatic impairment, the dose should be reduced accordingly while monitoring the blood levels. Especially patients with impaired hepatic and/or renal function have an increased risk of CNS toxicity after a treatment with high dose cytarabine. Hepatic and renal function and uric acid levels should be regularly monitored. In patients with pre-existing hepatic dysfunction, cytarabine should be used with care, at a reduced dose, and only after a strict risk-benefit analysis.

Following experimental high-dose cytarabine therapies in combination with cyclophosphamide as preparation for a bone marrow transplant, cases of cardiomyopathy and resulting deaths were reported.

Large fluid intake is indicated.

High-dose cytarabine treatment should only be given to patients aged over 60 after especially careful risk-benefit analysis.

Contraceptive measures
Cytarabine can have mutagenic effects. Men should therefore not father children during treatment and for up to six months after end of treatment. Furthermore, they should be informed before treatment about the possibility of sperm preservation, as cytarabine therapy may cause irreversible infertility.

If patients wish to have children after completing therapy, genetic counselling is strongly recommended.

Severe gastrointestinal undesirable effects require anti-emetic and other supportive measures.

Treatments with high doses require regular monitoring of CNS and lung function by a physician experienced in this type of treatment.

In order to prevent ophthalmological complication, the eyes should be rinsed regularly during high-dose treatment.

In cases of severe bone marrow suppression, the patients should be transferred to a sterile isolation room.

Immunosuppressive effects/increased susceptibility to infections
In patients with immunosuppression due to chemotherapeutic drugs like cytarabine, the administration of live vaccines can lead to severe or life-threatening infections.
During cytarabine therapy, no vaccinations with live vaccines should be performed. Dead vaccines or inactivated vaccines can be administered, however the response to these vaccines may be reduced.

Like other tumour-inhibiting substances, cytarabine treatment bears the risk of bleeding complications and severe infections due to bone marrow suppression. During high-dose therapy, CNS disorders, gastrointestinal disorders, hepatic dysfunction, skin reactions and eye disorders may occur.

If signs of CNS toxicity appear, or an allergy, a thorough risk-benefit evaluation should be performed.

Contact with skin and mucosa, especially in the area around the eyes, should be avoided.

Cytarabine is a teratogenic and mutagenic substance.

The enzyme dihydropyrimidine dehydrogenase (DPD) plays an important role in breaking down 5-FU. Nucleoside analogues, e.g. brivudine and sorivudine, may increase the plasma concentration of 5-FU and other fluoropyrimidines, thereby causing a marked increase in toxicity.

Furthermore, at least 4 weeks must pass between treatment with Alexan and brivudine, sorivudine, and analogues.

If applicable, determination of DPD enzyme activity is indicated prior to the treatment with Alexan. In case of an inadvertent administration of brivudine to patients receiving Alexan, effective measures should be taken to reduce the fluorouracil toxicity. Immediate hospitalisation is recommended. All measures should be initiated to prevent systemic infections and dehydration.

Patients receiving phenytoin together with Alexan should be regularly investigated for elevated phenytoin plasma levels.

Pancreatitis
Cases of pancreatitis have been observed after cytarabine use.

Neurology
Cases of severe neurological undesirable effects, ranging from headache to paralysis, coma, and stroke-like episodes, were observed mainly in children and adolescents receiving intravenous cytarabine in combination with intrathecal methotrexate.

Paediatric population
Safety in infants was not proven.

Alexan contains sodium:
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. it is essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Following previous therapy with L-asparaginase, cytarabine can lead to acute pancreatitis.

Myelotoxic interactions with other treatment methods which may have a toxic effect on the bone marrow (especially other cytostatics and radiation therapy) must be expected according to the current co-medication.

5-fluorocytosine

5-fluorocytosine should not be administered with cytarabine as the therapeutic efficacy of 5-fluorocytosine has been shown to be inhibited during such therapy. Limited data indicates that cytarabine may antagonise the anti-infective effect of 5-fluorocytosine, possibly through competitive inhibition of the anti-infective intake by fungi.

Cardiac glycosides

The gastrointestinal absorption of oral digoxin tablets can be significantly reduced in patients receiving a combined chemotherapy (including cytarabine chemotherapy), possibly due to transient damage of the intestinal mucosa by cytostatics.

In patients who received beta-acetyldigoxin and chemotherapeutic treatment with cyclophosphamides, vincristine and prednisone with or without cytarabine or procarbazine, a reversible decrease in steady-state digoxin levels and reduced renal glycoside elimination occurred. Limited data suggest that the extent of gastrointestinal absorption of digitoxin is not significantly affected by concomitant administration of combined chemotherapy known to decrease digoxin absorption. Therefore, plasma digoxin levels should be monitored in patients receiving similar chemotherapeutic combined treatments. The use of digitoxin in these patients can be considered as an alternative.

Anti-infectives

An *in-vitro* interaction study of gentamicin and cytarabine showed a cytarabine-related antagonism regarding the susceptibility of *K. pneumoniae* strains. In patients receiving cytarabine who were treated with gentamicin for a *K. pneumoniae* infection, the lack of immediate response to gentamicin may require a re-evaluation of the antibacterial therapy.

Methotrexate

Intravenous cytarabine administered concomitantly with intrathecal methotrexate may increase the risk of severe neurological undesirable effects such as headaches, paralysis, coma, and stroke-like episodes (see section 4.4).

Furthermore, at least 4 weeks must pass between treatment with Alexan and brivudine, sorivudine, and analogues.

If applicable, determination of DPD enzyme activity is indicated prior to the treatment with Alexan.

In concomitant administration of phenytoin and Alexan, an increase of phenytoin plasma concentration has been reported, resulting in symptoms of phenytoin intoxication (see also section 4.4).

Cytarabine can interfere with the determination of the protein fraction in the cerebrospinal fluid by turbidimetry (turbidity measurement) or by the Folin-Ciocalteu method.

4.6 Fertility, pregnancy and lactation

Pregnancy

During pregnancy Alexan should only be administered after a particularly strict indication, while carefully considering the risk/benefit ration for the mother and the foetus.

As cytarabine has shown mutagenic and teratogenic effects in certain animals, the possibility of pregnancy must be ruled out. Cytarabine is only to be used in women who are pregnant or could become pregnant after a careful consideration of the possible risks and benefits.

Due to the potential for anomalies in cytotoxic therapy, especially during the first trimester, the patient who is or may become pregnant during cytarabine treatment should be informed about the potential risk for the foetus and the advisability of continuing the pregnancy. There is a clear although significantly reduced risk if the therapy is started in the second or third trimester. Although normal infants were born by patients who were treated in all three trimesters, follow-up care for such infants is advisable.

Sufficient contraception must be provided to male and female patients of child-bearing age during and 6 months after treatment with Alexan.

If a pregnancy occurs during Alexan therapy, genetic counselling must be provided (see section 5.3).

Breast-feeding
Cytarabine must not be used during breast-feeding.

Breast-feeding must be discontinued before beginning treatment with Alexan.

Fertility
Fertility studies to evaluate the reproductive toxicity of cytarabine have not been conducted. In patients receiving cytarabine (especially in combination with alkylating agents), gonadal suppression leading to amenorrhoea and azoospermia may occur. In general, the effects seem to be connected to the dose and the duration of the therapy and irreversible (see section 4.8). As cytarabine has mutagenic potential that can lead to severe chromosomal damage in male spermatozoa, men treated with cytarabine and their partners should be instructed to use reliable contraceptive methods. Men should not father children during treatment and for up to six months after completion of treatment. Furthermore, they should be informed before treatment about the possibility of sperm preservation, as cytarabine therapy may cause irreversible infertility.

4.7 Effects on ability to drive and use machines

Cytarabine has no effect on the ability to drive or use machines. However, in patients receiving chemotherapy the ability to drive or use machines may be impaired due to undesirable effects. Patients should therefore be informed and instructed not to perform such activities if possible.

4.8 Undesirable effects

The undesirable effects caused by cytarabine depend on the posology, method of administration and duration of therapy.

The most common undesirable effects are gastrointestinal. Cytarabine has a toxic effect on the bone marrow, causing haemorrhagic undesirable effects.

Blood and lymphatic system disorders: Since cytarabine has a myelosuppressive effect, anaemia, leukopenia, thrombocytopenia, megaloblastic anaemia and reticulocyte reduction are to be expected as a result of administration of the medicinal product. The severity of these reactions depends on the dose and therapy regimen. Morphological cell changes to the bone marrow and peripheral blood count can be expected.

Cytarabine syndrome has been described. It is characterized by fever, myalgia, bone pain, occasional thoracic pain, maculopapular rash, conjunctivitis and malaise. It generally occurs 6−12 hours after administration of the medicinal product.
Corticosteroids have proved useful in the treatment or prevention of this syndrome. If the symptoms are serious enough to justify treatment, both corticosteroids and the continuation of cytarabine therapy should be considered.

The following definitions apply to the frequency terminology used hereafter:

Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1,000, <1/100)
Rare (≥1/10,000, <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations
Viral, bacterial, fungal, parasitic or saprophytic infections of the whole body may be associated with the use of cytarabine alone or in combination with other immunosuppressant agents (in immunosuppressive doses which affect the cellular or humoral defences). These infections may be mild, but they can also be severe and occasionally fatal.

Very common:
Sepsis (immunosuppression), pneumonia, infection

Not known:
Cellulitis at the injection site, liver abscess

Blood and lymphatic system disorders
Very common:
Myelosuppression, blood cell abnormalities (leukopenia, thrombocytopenia, anaemia, megaloblastic anaemia, and reticulocytopenia) are dose dependent.
At conventional doses, leukopenia occurs with a nadir on days 12 to 24. The high-dose therapy is linked to pronounced myelotoxicity.

Metabolism and nutrition disorders
Common:
Anorexia, hyperuricaemia as a consequence of rapid lysis of neoplastic cells. Like all other cytostatics, cytarabine may cause hypocalcaemia and secondary hyperuricaemia due to cell breakdown, which may require appropriate countermeasures.

Nervous system disorders
Central nervous system disorders are mostly observed in high-dose therapy.
At total doses of below 36 g cytarabine/m^2, toxic reactions of the CNS are rare. Predisposing factors include high age, renal and hepatic insufficiency, previous CNS treatment (irradiation, intrathecal cytostatic applications) and alcohol abuse.
The central nervous system disorders are mostly reversible.

Common:

Cerebral/cerebellar disorders (nystagmus, dysarthria, ataxia, confusion and personality changes), thinking and movement process disorders, somnolence, lethargy, coma, tremor, convulsions and anorexia

Uncommon:
Peripheral neuropathy

Rare:
Intrathecal application of cytarabine may lead to nausea, vomiting, fever and/or other symptoms of arachnoiditis. These symptoms can also be the consequence of a lumbar puncture. These symptoms are often mild and reversible. The intrathecal administration of cytarabine in doses of more than 30 mg/m^2 BSA often leads to neurotoxic reactions. In particular, short dosing intervals may lead to cumulative neurotoxicity (see also section 4.2).

Very rare:
Isolated cases of necrotizing leukoencephalopathy, myelopathy up to paraplegia or quadriplegia, and vision loss were described following intrathecal application of cytarabine. The intrathecal application of benzyl alcohol or other solubilizing additives must absolutely be avoided.

Not known:
Neurotoxicity, vertigo, headache, neuritis, and – following high doses – isolated cases of peripheral nerve lesions have been described, as well as cases of delayed progressive ascending paralysis, meningitis and encephalitis.

Eye disorders
Very common:
Conjunctivitis (in high-dose therapy)

Common:
Conjunctivitis, keratitis, photophobia, stinging eyes and vision disturbances are dose dependent and have been reported in 25 to 80% of the patients undergoing high-dose therapy.
Reversible haemorrhagic conjunctivitis (photophobia, burning, vision disturbances, increased lacrimation), ulcerative keratitis.
These effects can be prevented or decreased by frequently rinsing the eyes or the prophylactic use of eye drops.

Cardiac disorders
Uncommon:
Acute pericarditis

Very rare:
Damage to the myocardium, transient heart rhythm disorders

Not known:
Sinus bradycardia

Respiratory, thoracic and mediastinal disorders
Uncommon:
Dyspnoea, sore throat

Pulmonary oedema due to increased permeability of the alveolar capillaries was uncommon at the conventional dose and observed in approximately 10 to 30% of the patients following high cytarabine doses. These pulmonary complications are reversible in most cases. Difficulty breathing, pneumonia and lung toxicity occurred.

Patients receiving the average doses (1 g of cytarabine/m^2 BSA) concomitantly with other cytostatics developed diffuse interstitial pneumonia in 10 out of 52 cases. No causal correlation to the use of cytarabine has been found.

Gastrointestinal disorders

Common:

Abdominal pain, diarrhoea, dysphagia, mucositis, mucous ulceration (oral, anal) especially in the case of high-dose treatment; severe diarrhoea with corresponding potassium and protein loss, nausea and vomiting (especially after rapid intravenous injection).

Uncommon:

Oesophagitis, oesophageal ulceration, severe changes to the gastrointestinal mucous membranes with ulcerations, intestinal wall emphysema and infections may occur. This may lead to necrosis of the colon and necrotising colitis.

Especially in cases of high-dose therapy, cystoid pneumatosis and intestinal necrosis with ileus and peritonitis may occur.

Very rare:

Pancreatitis

Hepatobiliary disorders

Very common:

Hepatic dysfunction with an increase in cholestasis-indicating enzymes and hyperbilirubinaemia were observed in 25 to 50% of the patients under high-dose treatment.

Very rare:

Hepatomegaly

There have been individual reports of the occurrence of hepatic vein thrombosis (Budd-Chiari syndrome).

Not known:

Jaundice

Skin and subcutaneous tissue disorders

Very common:

Rash

Common:

Reversible undesirable skin reactions such as maculopapular exanthema, ulceration, erythrodermia, erythema, urticaria, vasculitis, mottled skin and pruritus.

At high doses, exfoliative dermatitis and alopecia may occur.

Following high doses of cytarabine, up to 75% of patients develop generalised erythema, sometimes with blistering and desquamation.

Uncommon:
Lentigo, skin ulceration, pruritus, burning pain on the palms and soles

Very rare:
Neutrophilic eccrine hidradenitis

Not known:
Palmar-plantar erythrodysaesthesia syndrome

Musculoskeletal and connective tissue disorders
Uncommon:
Myalgia and/or arthralgia were observed following high doses of cytarabine

Very rare:
The occurrence of rhabdomyolysis has been described.

Renal and urinary disorders
Common:
Urinary retention, renal dysfunction

An increase in plasma creatinine was observed in 5-20% of the patients in high dose cytarabine therapy but a causal connection to cytarabine could not be proven.

In case of massive cell degeneration, measures should be taken to prevent uric acid nephropathy.

General disorders and administration site conditions
Common:
Inflammation of the throat, allergic oedema, gonadal dysfunction, chest pains, ascites, immunosuppression, sepsis, thrombophlebitis and haemorrhage, thrombophlebitis at the injection site.
Fever occurs in 20−50% of the patients receiving high-dose therapy.

Very rare:
Immediate allergic reactions (urticaria, anaphylaxis) are very rare. One case of anaphylaxis was reported, which led to cardiopulmonary arrest, requiring resuscitation measures. This occurred immediately after IV administration of cytarabine.
The syndrome of inappropriate adiuretic hormone secretion was reported in patients undergoing high-dose treatment with cytarabine.

Cytarabine (Ara-C) syndrome
This syndrome, which has been described in the literature, is marked by fever, myalgia, bone pains, occasional chest pains, maculopapular exanthema, conjunctivitis and nausea. It generally occurs 6−12 hours after administration. Corticosteroids have proven effective in treating or preventing the syndrome. If corticosteroids are effective, the continuation of cytarabine therapy can be considered.

Undesirable effects in high-dose cytarabine therapy that were not observed at conventional doses:
Haematological toxicity

This is expressed as profound pancytopenia, which lasts for 15−25 days and is linked to a stronger bone marrow aplasia than is observed at conventional doses.

Nervous system disorders
Following treatment with high doses of cytarabine, cerebral or cerebellar symptoms such as personality changes, impaired attention, dysarthria, ataxia, tremor, nystagmus, headache, confusion, drowsiness, dizziness, coma, and convulsions occurred in 3−37% of patients. The incidence may be higher in elderly patients (>55 years). Other predisposing factors are hepatic or renal impairment, previous CNS treatment (e.g. radiation therapy) and alcohol abuse. CNS disorders are reversible in most cases.

The risk of CNS toxicity is increased if cytarabine treatment (high dose, IV) is combined with another CNS-toxic therapy, such as radiation therapy or high-dose therapy.

Corneal and conjunctival toxicity
Reversible lesions of the cornea and haemorrhagic conjunctivitis have been described. These can be prevented or reduced by use of corticosteroid-containing eye drops.

Gastrointestinal disorders
Especially in high-dose treatment with cytarabine, severe reactions may occur in addition to the normal symptoms. Intestinal perforation, pneumatosis cystoides intestinalis or necrosis with ileus and peritonitis have been reported.

Liver abscesses, Budd-Chiari syndrome (hepatic venous thrombosis) and pancreatitis have been reported following high-dose therapy.

Respiratory, thoracic and mediastinal disorders
Clinical signs such as pulmonary oedema/ARDS may develop, especially in high-dose therapy. This reaction is probably caused by damage to alveolar capillaries. It is difficult to determine the frequency (reported as 10−26% in various publications), since the patients were usually in relapse and other factors may have contributed to this response.

Others
Following cytarabine therapy, cardiomyopathy and rhabdomyolysis have been reported. One case of anaphylaxis has been reported, leading to a cardiopulmonary arrest, requiring resuscitation. This case occurred directly following intravenous administration of cytarabine.

Gastrointestinal undesirable effects are reduced if cytarabine is administered as an infusion. Local glucocorticoids are recommended as prophylaxis for haemorrhagic conjunctivitis.

Amenorrhoea and azoospermia (see section 4.6).

The following undesirable effects were observed following intrathecal administration:
Expected systemic reactions: Bone marrow depression, nausea, vomiting. In some patients, severe spinal toxicity, which could even lead to quadriplegia and paralysis, necrotising encephalopathy, blindness and other isolated neurotoxicity were reported.

In cases of high-dose continuous infusion (more than 200 mg/m² BSA/day over 5–7 days), undesirable effects were more pronounced than in standard therapy.

Polyserositis and early deaths due to uncontrollable haemorrhage or septicaemia and death due to prolonged bone marrow depression. The maximum tolerable dose in humans was determined as 4.5 g/m^2. In doses of more than 3 g/m^2 the cerebral toxicity is much more pronounced.

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. 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

Symptoms of intoxication

A chronic overdose may lead to severe bone marrow depression, which may cause massive haemorrhages and life-threatening infections, as well as neurotoxicity.

The myelotoxicity of cytarabine is dose-limiting. Even within a high-dose treatment with cumulative doses of approximately 18 to 36 g of cytarabine per treatment cycle, severe bone marrow toxicity up to myelophthisis should be expected. This is only fully clinically identifiable after 1 to 2 weeks. It depends on both the dose and other factors, such as age, the clinical condition and bone marrow reserves of the patient, and on additional myelotoxic therapy.

Twelve doses of 4.5 mg/m^2 by intravenous infusion, administered over the course of one hour every 12 hours, led to irreversible and fatal CNS toxicity.

Treatment of intoxication

There is no known specific antidote to cytarabine.
If intoxication occurs, immediate discontinuation of the cytarabine therapy and careful monitoring of the patient is required.
An accidental severe overdose during intrathecal use requires immediate replacement of the cerebrospinal fluid with isotonic sodium chloride solution.
Even if an overdose is only suspected, blood counts must be closely monitored for a long period.
Corresponding supportive measures should be taken (e.g. blood transfusion or platelet transfusion, antibiotics).

Cytarabine can be removed by haemodialysis. There is no information available regarding the effect in cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Antimetabolites, Pyrimidine analogues, ATC code: L01BC01

Alexan contains cytarabine (4-amino-1- (β-D-arabinofuranosyl) -1 H-pyrimidin-2-one), a cytostatic agent belongs to the antimetabolite group. It differs from the body's own pyrimidine nucleoside

cytidine and 2'-deoxycytidine only in the sugar residue (arabinose instead of ribose), that is, it is a pyrimidine analogue.

The active cytarabine nucleotides inhibit DNA synthesis in the S-phase of the cell cycle. The proposed molecular mechanisms of action for this effect are inhibition of cytidine phosphate reductase, incorporation into DNA and RNA leading to the dysfunction of these nucleic acids and inhibition of DNA polymerase. In particular, the virally-induced RNA-dependent DNA polymerase (reverse transcriptase) is strongly inhibited. The ability of cytarabine to recruit resting cells (G_0 phase) into the proliferation cycle, making these cells susceptible to the chemotherapeutic effect of cell phase-specific cytostatic agents, probably contributes to the cytostatic effect of cytarabine.

The susceptibility of a tissue to cytarabine is dependent on the relationship between its cytidine deaminase and cytidine kinase activity. In the course of treatment with cytarabine, both pre-existing and acquired resistance to this cytotoxic agent is observed, which is attributed to the ratio of the said enzymes in the tumour tissue.

5.2 Pharmacokinetic properties

Following uptake into the cells via the pyrimidine nucleoside transport mechanism, cytarabine is deaminated into the inactive uracil arabinoside on the one hand and phosphorylated into the active nucleotide on the other hand (cytarabine mono-, di- and triphosphate).

The pharmacokinetic properties of cytarabine are determined by its high water solubility and its low lipid solubility. The medicinal product is to be administered parenterally. After the initial distribution phase, the plasma level decreases with a half-life of 2−2.5 hours. In this second phase of elimination, about 80% is in the form of the inactive uracil arabinoside. Within 24 hours, 80% of the administered dose is eliminated through urine, predominantly in the form of uracil arabinoside. In cerebrospinal fluid, the concentrations of cytarabine following intravenous administration are, as a rule, 40% of those in blood plasma. In intrathecal administration, the level of cytarabine in cerebrospinal fluid decreases with a half-life of 2−11 hours, whereby, due to the lower deaminase activity in cerebrospinal fluid, predominantly unchanged cytarabine is available.

The kinetics of cytarabine blood levels remain constant following repeated administration and are not affected by corticosteroids and other cytostatics.

In IV infusion, a constant, dose-dependent blood levels are achieved after 30−60 minutes.

Following subcutaneous administration, peak plasma levels are achieved after 20−60 minutes. At comparable doses, they are markedly lower than plasma levels achievable by intravenous administration.

5.3 Preclinical safety data

a) Subchronic and chronic toxicity
With regard to subchronic toxicity, animal studies predominantly observed bone marrow depression with blood count changes and damage to the intestinal mucosa.

There are no studies of the chronic toxicity of cytarabine.
b) Mutagenic and carcinogenic potential:

Cytarabine was shown to be mutagenic in animal models. In humans, chromosomal defects in peripheral lymphocytes occurred following cytarabine treatment.
It has been shown that cytarabine is carcinogenic in animals. The possibility of similar effects in humans should be considered when planning long-term therapy.

c) Reproductive toxicity
Cytarabine has been shown to have teratogenic effects in various animal species. Abnormalities of the skeleton, the eyes, the brain and the kidneys have been observed. There is insufficient data on humans. The malformations observed so far were at the extremities, the outer ear and the ear canal. An exposure in the third trimester of pregnancy can lead or contribute to delayed growth and pancytopenia in the fetus/neonate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium lactate solution, 60%
Lactic acid
Water for injection.

6.2 Incompatibilities

Cytarabine solutions for injection or infusion are incompatible with 5-fluorouracil, heparin, gentamicin, insulin, methotrexate, methylprednisolone, nafcillin, oxacillin and penicillin G. As further incompatibilities are possible, mixing with other pharmaceuticals should generally be avoided.

The medicinal product must not be mixed with medicinal products other than those listed in section 6.6.

6.3 Shelf life

Unopened package:
The expiry date of the product is indicated on the packaging materials

After first opening:
Alexan is stable for 28 days after opening, stored at -20°C (with protection of light), 5°C+/-3°C (with protection of light), and at room temperature (20–25°C) with light protection and under influence of light.

After dilution:
A suitable infusion solution can be prepared by dilution of Alexan 50 mg/ml with 0.9% sodium chloride solution, 5% glucose solution and Ringer´s solution.
The maximum storage time for Alexan infusion solutions with a concentration of 20.0 mg/ml and of 0.1 mg/ml prepared in sodium chloride 0.9% is 28 days, stored in a refrigerator (2–8°C) with protection of light, and at room temperature (20–25°C) with or without light protection.
The maximum storage time for Alexan infusion solutions with a concentration of 20.0 mg/ml prepared in 5% glucose is 28 days, stored in a refrigerator (2–8°C) with protection of light, and at room temperature (20–25°C) with or without light protection.

The maximum storage time for Alexan infusion solutions with a concentration of 0.1 mg/ml prepared in 5% glucose is 28 days stored in a refrigerator (2–8°C) with protection of light, and 14 days stored at room temperature (20–25°C) with or without light protection.
The maximum storage time for Alexan infusion solutions with a concentration of 5.0 mg/ml prepared in Ringer´s solution in syringe of polypropylene is 2 days for all tested storage conditions (2–8°C with light protection, 20–25°C with or without light protection).
Stability studies results showed no influence from the container of the infusion vehicle (PVC bags, PP bags and glass bottles).
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 normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25°C.
Keep in the original package in order to protect from light.

6.5 Nature and contents of container

For 50 mg/ml:
1 x 10 ml vials
1 x 20 ml vials
1 x 40 ml vials

Glass vials (type 1) with grey fluoropolymer coated rubber stoppers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For infusion, Alexan can be diluted with physiological saline solution, 5% glucose solution or Ringer's solution.

If Alexan comes into contact with the skin, the affected site should be rinsed with copious amounts of water and then thoroughly washed with water and soap. If the solution comes into contact with the eyes, the eyes should be carefully rinsed with copious amounts of water, and an ophthalmologist should be consulted immediately.

Pregnant personnel should not come into contact with this medicinal product.

Alexan should not be used after its expiration date.

After use, the bottle and the injection material (including gloves) should be disposed of according to the regulations for cytostatics. Any remaining medicine and the primary packaging must be disposed of as hazardous waste.

7. MARKETING AUTHORISATION HOLDER AND IMPORTER

Novartis Israel Ltd.,
P.O.Box 7126,
Tel Aviv, Israel

8. MARKETING AUTHORISATION NUMBER

Alexan: Marketing Authorisation Number: 133-79-27970-00

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