SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cytarabine STADA 20 mg/ml, solution for injection
Cytarabine STADA 50 mg/ml, solution for infusion
Cytarabine STADA 100 mg/ml, concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cytarabine STADA 20 mg/ml: 1 ml solution contains 20 mg cytarabine.
Cytarabine STADA 50 mg/ml: 1 ml solution contains 50 mg cytarabine.
Cytarabine STADA 100 mg/ml: 1 ml solution contains 100 mg cytarabine.

Excipients with known effect
Cytarabine STADA 20 mg/ml: 1 ml solution contains 2.6 mg sodium.
Cytarabine STADA 50 mg/ml: 1 ml solution contains 2.56 mg sodium.
Cytarabine STADA 100 mg/ml: 1 ml solution contains 5.13 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

20 mg/ml: Solution for injection;50 mg/ml: Solution for infusion: Clear, colourless solution

100 mg/ml: Concentrate for solution for infusion: Clear, colourless to yellowish solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute leukaemia in children and adults, including prophylaxis and treatment of CNS-involvement (meningeal leukaemia).

4.2 Posology and method of administration

Posology
Treatment with Cytarabine STADA should be initiated by, or be in consultation with, a doctor with extensive experience in treatment with cytostatics. Only general recommendations can be given, as acute leukaemia today is almost exclusively treated with combinations of cytostatics, when 2-5 different products are included. The dose must be determined individually and exactly in relation to body surface area (BSA). The treatment is administered repeatedly, and the best results have been achieved with combinations of cytostatics, where Cytarabine STADA is administered for 7-10 days.

Induction treatment: 100 mg/m² /24 hours, as continuous infusion for 7 days in combination with other cytostatics including for instance an anthracycline. Additional cycles may be administered at intervals of 2-4 weeks, until remission is achieved or unacceptable toxicity occurs.

Maintenance treatment: Maintenance dosage and schedule vary depending on the regimen used. Cytarabine has been administered in doses of 100-200 mg/m², as continuous infusion for 5 days at monthly intervals as monotherapy or in combination with other cytostatics.

Intrathecally: Doses between 5 and 30 mg/m^2 BSA have been administered. Usually a dose of 30 mg/m^2 BSA is given once every 4 days until cerebrospinal fluid findings are normal, followed by one additional dose. The injection should be slow. See 4.8.

High dosage: Cytarabine STADA is administered as monotherapy or in combination with other cytostatics, 2-3 g/m^2, as intravenous infusion, for 1-3 hours every 12 hours for 2-6 days. A total treatment dose of 36 g/m^2 should not be exceeded. See 4.4 and 4.8.

Renal or hepatic impairment
Dosage should be reduced.

Elderly
High dose therapy in patients > 60 years should be administered only after careful risk-benefit-evaluation.

Paediatric patients:
The safety of cytarabine for use in infants is not established.

Method of administration
Cytarabine STADA 20 mg/ml, solution for injection is intended for intravenous, intramuscular, subcutaneous and intrathecal use.

Cytarabine STADA 50 mg/ml, solution for infusion and 100 mg/ml, concentrate for solution for infusion are intended for intravenous use only.

4.3 Contraindications

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

Anaemia, leukopenia and thrombocytopenia of non-malignant aetiology (e.g. bone marrow aplasia); unless the clinician feels that such management offers the most hopeful alternative for the patient.

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

4.4 Special warnings and precautions for use

Paediatric patients
The safety of cytarabine for use in infants is not established.

Warnings
Cytarabine is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving this drug must be under close medical supervision and, during induction therapy, should have leukocyte and platelet counts performed daily. 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).

Anaphylactic reactions have occurred with cytarabine treatment. One case of anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine.

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following some experimental cytarabine dose schedules. These reactions include reversible corneal toxicity; cerebral and cerebellar dysfunction, usually reversible; somnolence; convulsion; severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis, leading to peritonitis; sepsis and liver abscess; and pulmonary oedema.

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.

Precautions

Patients receiving cytarabine must be monitored closely. Frequent platelet and leukocyte counts are mandatory. 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.

Peripheral motor and sensory neuropathies after consolidation with high doses of cytarabine, daunorubicin, and asparaginase have occurred in adult patients with acute non lymphocytic leukaemia. Patients treated with high doses of cytarabine should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders.

Severe and sometimes fatal pulmonary toxicity, adult respiratory distress syndrome and pulmonary oedema have occurred following high dose schedules with cytarabine therapy.

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.

Abdominal tenderness (peritonitis) and guaiac positive colitis, with concurrent neutropenia and thrombocytopenia, have been reported in patients treated with conventional doses of cytarabine in combination with other drugs. Patients have responded to non-operative medical management.

Delayed progressive ascending paralysis resulting in death has been reported in children with AML following intrathecal and intravenous cytarabine at conventional doses in combination with other drugs.

Patient with pre-existing hepatic impairment

Both hepatic and renal function should be monitored during cytarabine therapy. In patients with pre-existing liver impairment, cytarabine should be administered only with utmost care.

Periodic checks of bone marrow, liver and kidney functions should be performed in patients receiving cytarabine.

Like other cytotoxic drugs, cytarabine may induce hyperuricaemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacological measures as may be necessary to control this problem.

Vaccine/Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cytarabine may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving cytarabine. Killed or

inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

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

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

Cases of cardiomyopathy with subsequent death has been reported following experimental high dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation.

Excipients
Cytarabine STADA 20 mg/ml contains 2.6 mg (0.114 mmol) sodium per ml of undiluted solution, equivalent to 0.13 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

Cytarabine STADA 50 mg/ml contains 2.56 mg (0.112 mmol) sodium per ml of undiluted solution, equivalent to 0.13 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

Cytarabine STADA 100 mg/ml contains 5.13 mg (0.224 mmol) sodium per ml of undiluted solution, equivalent to 0.26 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

Digoxin
Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyldigoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without cytarabine or procarbazine. Steady-state plasma digitoxin concentrations did not appear to change. Therefore, monitoring of plasma digoxin levels may be indicated in patients receiving similar combination chemotherapy regimens. The utilisation of digitoxin for such patients may be considered as an alternative.

Gentamicin
An *in-vitro* interaction study between gentamicin and cytarabine showed a cytarabine related antagonism for the susceptibility of K. pneumoniae strains. In patients on cytarabine being treated with gentamicin for a K. pneumoniae infection, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

Use of cytarabine alone or in combination with other immunosuppressive agents
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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Cytarabine is known to be teratogenic in some animal species. The use of cytarabine in women who are, or who may become, pregnant should be undertaken only after due consideration of the potential benefits and hazards.
Men and women have to use effective contraception during and up to 6 months after treatment.

Breast-feeding
This product should not normally be administered to patients who are pregnant or to mothers who are breast-feeding.

Fertility
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 (see section 4.8). Given that cytarabine has a mutagenic potential which could induce chromosomal damage in the human spermatozoa, males undergoing cytarabine treatment and their partner should be advised to use a reliable contraceptive method during and up to 6 months after treatment.

4.7 Effects on ability to drive and use machines

Cytarabine has no influence on the ability to drive and use machines. Nevertheless, patients receiving chemotherapy may have an impaired ability to drive or operate machinery and should be warned of the possibility and advised to avoid such tasks if so affected.

4.8 Undesirable effects

The following adverse events have been reported in association with cytarabine therapy:

Frequencies are defined using the following convention:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000),
Not known (cannot be estimated from the available data)

Undesirable effects from cytarabine are dose-dependent. Most common are gastrointestinal undesirable effects. Cytarabine is toxic to the bone marrow, and causes haematological undesirable effects.

Infections and infestations
Uncommon: Sepsis (immunosuppression), cellulitis at injection site, pneumonia.
Not Known: Liver abscess

Neoplasm benign, malignant and unspecified (Incl. cysts and polyps)
Uncommon: Lentigo.

Blood and lymphatic system disorders
Common: Anaemia, megaloblastosis, leukopenia, thrombocytopenia.
Not Known: Reduced reticulocytes

The severity of these reactions is dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

Immune system disorders

Uncommon: Anaphylaxis.
Not known: Allergic oedema

Metabolism and nutrition disorders
Common: Anorexia, hyperuricaemia.

Nervous system disorders
Common: At high doses cerebellar or cerebral influence with deterioration of the level of consciousness, dysarthria, nystagmus.
Uncommon: Headache, peripheral neuropathy, paraplegia at intrathecal administration
Not known: Neural toxicity, neuritis, dizziness

Eye disorders
Common: Reversible haemorrhagic conjunctivitis (photophobia, burning, visual disturbance, increased lacrimation), keratitis.
Not known: Conjunctivitis (may occur with rash)

Cardiac disorders
Uncommon: Pericarditis
Very rare: Arrhythmia.

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

Gastrointestinal disorders
Common: Dysphagia, abdominal pain, nausea, vomiting, diarrhoea, oral / anal inflammation or ulceration.
Uncommon: Esophagitis, oesophageal ulceration, pneumatosis cystoides intestinalis, necrotising colitis, peritonitis
Not known: Pancreatitis

Hepatobiliary disorders
Common: Reversible effects on the liver with increased enzyme levels.
Uncommon: Jaundice.
Not known: Hepatic dysfunction

Skin and subcutaneous tissue disorders
Common: Reversible undesirable effects to the skin, such as erythema, bullous dermatitis, urticaria, vasculitis, alopecia.
Uncommon: Skin ulceration, pruritus, burning pain of palms and soles.
Very rare: Neutrophilic eccrine hidradenitis.
Not known: Freckling, rash

Musculoskeletal and connective tissue disorders
Uncommon: Myalgia, arthralgia.

Renal and urinary disorders
Common: Renal impairment, urinary retention

General disorders and administration site conditions
Common: Fever, thrombophlebitis at the injection site.
Uncommon: Chest pain.

Cytarabine (Ara-C) Syndrome: (Immunoallergic effect):
Fever, myalgia, bone pain, occasional chest pain, exanthema, conjunctivitis and nausea may occur 6-12 h after start of therapy. Corticosteroids may be considered as prophylaxis and therapy. If they are effective, therapy with cytarabine may be continued.

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

Haematological toxicity
Seen as profound Pancytopenia which may last 15-25 days along with more severe bone marrow aplasia than that observed at conventional doses.

Infections and infestations
Sepsis, liver abscess.

Nervous system disorders
After treatment with high doses of cytarabine, symptoms of cerebral or cerebellar influence like personality changes, affected alertness, dysarthria, ataxia, tremor, nystagmus, headache, confusion, somnolence, dizziness, coma, convulsions, etc. appear in 8-37 % of treated patients. 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.
Skin and subcutaneous tissue disorders: Skin rash leading to 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. These infections may be mild, but can be severe.
A cytarabine syndrome has been described. It is characterised by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6-12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are serious enough to warrant treatment, corticosteroids should be contemplated as well as continuation of therapy with cytarabine

Gastrointestinal disorders
Especially in treatment with high doses of cytarabine, more severe reactions may appear in addition to common symptoms. Intestinal perforation or necrosis with ileus and peritonitis have been reported.

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

Respiratory, thoracic and mediastinal disorders
Clinical signs as present in pulmonary oedema/ARDS may develop, particularly in high-dose therapy. The reaction is probably caused by an alveolar capillary injury. It is difficult to make an assessment of frequencies (stated as 10-26 % in different publications), since the patients usually have been in relapse where other factors may contribute to this reaction.

Others
Following cytarabine therapy, cardiomyopathy and rhabdomyolysis have been reported. One case of anaphylaxis that resulted in cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine.

The gastrointestinal undesirable effects are reduced if cytarabine is administered as infusion. Local glucocorticoides are recommended as prophylaxis of haemorrhagic conjunctivitis.

Amenorrhoea and azoospermia (see section 4.6).

The following side-effects have been reported with intrathecal use:
Expected systemic reactions: bone marrow depression, nausea, vomiting. Occasionally, severe spinal cord toxicity even leading to quadriplegia and paralysis, necrotising encephalopathy, blindness and other isolated neurotoxicities have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No specific antidote. Managed advised at overdosage include: Cessation of therapy, followed by management of subsequent bone marrow depression including whole blood or platelet transfusion and antibiotics as required. Twelve doses of 4.5 g/m^2 by IV infusion over one hour every 12 hours induces irreversible and fatal central nervous system toxicity.

Cytarabine may be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pyrimidine analogue
ATC code: L01BC01

Cytarabine, a pyrimidine nucleoside analogue, is an antineoplastic agent, which inhibits the synthesis of deoxyribonucleic acid specifically in the S phase of the cell cycle. It also has antiviral and immunosuppressant properties. Detailed studies on the mechanism of cytotoxicity in vitro suggests that the primary action of cytarabine is inhibition of deoxycytidine synthesis its active triphosphate metabolite arabinofuranosyl cytosine triphosphate ARA-CTP, although inhibition of cytidylic kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytocidal actions.

High dose cytarabine regimens can overcome the resistance of leukemic cells no longer responding to conventional doses. Several mechanisms appear to be involved to this resistance:
Increases in the quantity of substrate
Increase in the intracellular pool of ARA-CTP, since there is a positive correlation between intracellular retention of ARA-CTP and percentage of cells in S-phase.

5.2 Pharmacokinetic properties

Cytarabine is deaminated to arabinofuranosyl uracil in the liver and kidneys. After intravenous administration to humans, only 5.8 % of the administered doses is excreted unaltered in urine within 12-24 hours, 90 % of the dose is excreted as the inactive deaminated product, arabinofuranosyl uracil (ARA-U). Cytarabine appears to be metabolised rapidly, primarily by the liver and perhaps by the kidney. After single high intravenous doses, blood levels fall to unmeasurable levels within 15 minutes in most patients. Some patients have indemonstrable circulating drug as early as 5 minutes after injection. The half life of the drug is 10 minutes.

High dose cytarabine achieves plasma peak levels 200 fold higher than that observed with conventional dose regimen. The peak of inactive metabolite ARA-U, with high dose regimen, is observed after only 15 minutes. The renal clearance is slower with high dose cytarabine than with conventional dose cytarabine. The cerebrospinal fluid (CSF) levels achieved, after high dose 1-3 g/m^2 cytarabine intravenous infusion, are around 100-300 nanograms/ml.

Peak plasma levels are achieved about 20-60 minutes after subcutaneous application. At comparable doses, they are significantly lower than plasma levels achieved after intravenous administration.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

20 mg/ml
Sodium (S)-lactate solution
Sodium chloride
Water for injections

50 mg/ml
Sodium (S)-lactate solution
Water for injections

100 mg/ml
Sodium (S)-lactate solution
Water for injections

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products except for those mentioned under 6.6.

Incompatibilities with: Heparin, insulin, methotrexate, 5-fluorouracil, nafcillin, oxacillin, penicillin G, methyl-prednisolone succinate.

6.3 Shelf-life

2 years

In-use stability
Chemical and physical in-use stability after dilution in sodium chloride solution, 9 mg/ml or glucose solution, 50 mg/ml has been demonstrated for 10 days when stored in a refrigerator or at room temperature.

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 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25 °C.

No opened vial may be stored.

6.5 Nature and content of container

Vials of type I glass with stoppers of chlorobutyl, type I, and aluminium caps.
Package sizes:
20 mg/ml: 10 x 2 ml and 10 x 5 ml
50 mg/ml: 1 x 20 ml and 1 x 80 ml
100 mg/ml: 1 x 10 ml and 1 x 50 ml

6.6 Special precautions for disposal

Cytarabine STADA should for infusion be diluted with sodium chloride solution, 9 mg/ml, or glucose solution, 50 mg/ml. Use of the infusion solution with closed transmission systems is recommended. Solutions for dilution containing benzyl alcohol must not be used for intrathecal administration. The concentration must, however, not exceed 50 mg/ml.

If Cytarabine STADA comes in contact with skin, the exposed area should be rinsed with large amounts of water and then thoroughly washed with soap and water. If the solution gets into the eyes, rinse very carefully with large amounts of water, whereupon an eye specialist should be consulted immediately.

Pregnant staff should be excluded from working with this drug.

After use, bottles and injection materials, including gloves, should be disposed of according to the rules for cytostatics.
Inactivation of spilled or leaked drug can be obtained with 5 % sodium hypochlorite solution. All cleaning materials should be disposed of as indicated previously.

7. MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2-18
D-61118 Bad Vilbel
Germany

8. MARKETING AUTHORISATION NUMBER(S)

Cytarabine STADA 20 mg/ml, solution for injection: 16725
Cytarabine STADA 50 mg/ml, solution for infusion: 16726
Cytarabine STADA 100 mg/ml, concentrate for solution for infusion: 16727

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2002-10-29/2007-05-03

10. DATE OF REVISION OF THE TEXT

2020-07-10