# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

## VI.1 Elements for summary tables in the EPAR

### VI.1.1 Summary table of Safety concerns

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| Important identified risk (s) | • Bone marrow suppression (including leucopenia and thrombocytopenia)<br>• Infections (including neutropenic sepsis) |
| Important potential risk (s) | • Tumour Lysis Syndrome |
| Missing information | • Pregnancy and lactation<br>• Use in infants |

### VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Plan

Not applicable.

### VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

### VI.1.4 Summary table of risk minimisation measures

| **Safety concern** | **Routine risk minimisation measures** | **Additional risk minimisation measures** |
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| Important identified risk: Bone marrow | Accord product information (meant for prescribing physicians) for | Currently available data does not support the need for additional risk |

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| suppression (including leucopenia and thrombocytopenia) | cytarabine includes following information on this safety concern:<br>Section 4.2: Remission induction:<br>a) Continuous treatment:<br>i) Rapid injection - 2 mg/kg/day is a judicious starting dose. Administer for 10 days. Obtain daily blood counts. If no antileukaemic effect is noted and there is no apparent toxicity, increase to 4 mg/kg/day and maintain until therapeutic response or toxicity is evident. Almost all patients can be carried to toxicity with these doses.<br>Elderly Patients:<br>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.<br>Section 4.3: Therapy with Cytarabine should not be considered in patients with pre-existing drug- | minimization activities. |

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| | induced bone marrow suppression, unless the clinician feels that such management offers the most hopeful alternative for the patient. Cytarabine should not be used in the management of non-malignant disease, except for immunosuppression.<br><br>Section 4.4: 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 leucocyte and platelet counts performed daily. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood.<br><br>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). | |

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| | Patients receiving Cytarabine must be monitored closely. Frequent platelet and leucocyte 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.<br><br>Periodic checks of bone marrow, liver and kidney functions should be performed in patients receiving Cytarabine.<br><br>Section 4.8:<br><br>Undesirable effects from cytarabine are dose-dependent. Cytarabine is toxic to the bone marrow, and causes haematological undesirable | |

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| | effects.<br><br><u>Blood and lymphatic system disorders:</u><br><br>Common: Anaemia, megaloblastosis, leucopenia, thrombocytopenia.<br><br>Not Known: Reduced reticulocytes<br><br>The severity of these reactions is dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.<br><br>Cytarabine is not recommended for intrathecal use; however, the following side effects have been reported with such use. Expected systemic reactions: bone marrow depression, nausea, vomiting.<br><br>Section 4.9: At overdosage: Cessation of therapy, followed by management of subsequent bone marrow depression including whole blood or platelet transfusion and antibiotics as required. | |
| Important identified risk: Infections (including neutropenic sepsis) | Accord product information (meant for prescribing physicians) for cytarabine includes following information on this safety concern: | Currently available data does not support the need for additional risk minimization activities. |

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| | Section 4.4: Immunosuppressant Effects/Increased Susceptibility to Infections.<br><br>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.<br><br>Section 4.8:<br><br>Infections and infestations:<br><br>Uncommon: Sepsis (immunosuppression), cellulitis at injection site.<br><br>Not Known: Pneumonia, liver abscess<br><br>Skin and subcutaneous tissue disorders: 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 | |

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| | immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe. | |
| Important potential risk: Tumour Lysis Syndrome | Accord product information (meant for prescribing physicians) for cytarabine includes following information on this safety concern:<br><br>Section 4.4: 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.<br><br>Section 4.8: Metabolism and nutrition disorders:<br><br>Common: hyperuricaemia. | Currently available data does not support the need for additional risk minimization activities. |
| Missing information: Pregnancy and lactation | Accord product information (meant for prescribing physicians) for cytarabine includes following information on this safety concern:<br><br>Section 4.6: Cytarabine is known to be teratogenic in some animal species. The use of Cytarabine in | Currently available data does not support the need for additional risk minimization activities. |

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| | 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.<br>This product should not normally be administered to patients who are pregnant or to mothers who are breastfeeding. | |
| Missing information: Use in infants | Accord product information (meant for prescribing physicians) for cytarabine includes following information on this safety concern:<br>Section 4.4: The safety of this drug for use in infants is not established. | Currently available data does not support the need for additional risk minimization activities. |

## VI.2 Elements for a public summary

### VI.2.1 Overview of disease epidemiology

**Acute myeloid leukaemia (AML):**

The number of new cases of acute myeloid leukemia in adults in Europe is 5–8 cases/100 000 population /year. The mortality is approx 4–6 cases/100 000/year. [(2)] Acute myeloid leukemia (AML) accounts for approximately 25% of all leukemias in adults in the Western world, and therefore is the most frequent form of leukemia. Worldwide, the occurrence of AML is highest in the U.S., Australia, and Western Europe. AML is primarily a disease of later adulthood. Patients

newly diagnosed with AML have a median age of 65 years [3]. AML in adults has a slight male predominance in most countries. The development of AML has been associated with several risk factors. These include age, antecedent hematologic disease, and genetic disorders; as well as exposures to viruses as well as radiation, chemical, or other occupational hazards and previous chemotherapy. [2]

**Acute leukaemias:**

Acute lymphocytic leukemia (ALL) is uncommon in adults. About 10,000 new cases are diagnosed in adults in Europe each year. In adults, ALL represents about 15% of leukemias: the chronic form is five times more common. ALL affects white more than blacks, males more than females, and those in Western, affluent countries more than those in the developing countries. The number of new cases /year in Europe were 1.3 per 100,000 in men and 0.9 in women. In adults aged 15 and over, half the cases is under age 50, and ALL is rare over the age of 70. ALL is the most common malignancy in children, accounting for 30% of all cancers and 80% of all leukemias. In children almost two-thirds of the cases occur in age from 2 to 6 years.

Leukemia accounts for 30% of all cancers diagnosed in children less than 15 years of age in industrialized countries. [4] Common risk factors for ALL include genetic disorders and exposures to viruses as well as radiation, chemical, or other occupational hazards and previous chemotherapy. [5]

### VI.2.2 Summary of treatment benefits

Cytarabine is used for the treatment of acute myeloid leukaemia in adults and for other acute leukaemias of adults and children.

Accord has not conducted any studies for cytarabine on expected benefit considering its similarity to the currently marketed product (DepoCyte, Napp Pharmaceuticals Limited, United Kingdom).

### VI.2.3 Unknowns relating to treatment benefits

The efficacy and safety of cytarabine has not been established in pregnancy and infants.

### VI.2.4 Summary of safety concerns

**Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Bone marrow suppression (including leucopenia and thrombocytopenia) | Cytarabine strongly reduces blood cell production in the bone marrow. This can make you more prone to infections or bleeding. The blood cell numbers can continue to fall for up to a week after stopping treatment. Doctor will test your blood regularly and examine your bone marrow if required. [6] | Yes<br>Do not take cytarabine if you are already taking medicines that have caused you to have a low blood count caused by suppression of your bone marrow (tissue capable of making blood cells). [6] |
| Infections (including neutropenic sepsis) | Cytarabine strongly reduces blood cell production in the bone marrow. This can make you more prone to infections or bleeding. [6]<br>Possible side effects: [6]<br>Common:<br>Not enough white and red blood cells or blood platelets, which may make you more prone to infections or bleeding.<br>Others:<br>• Blood infection (sepsis)<br>• Viral, bacterial etc infections<br>Administration of live or live-attenuated vaccines in patients | Yes<br>Testing blood regularly and examine bone marrow if required. [6]<br>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. [1] |

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| | immunocompromised by chemotherapeutic agents including cytarabine, may result in serious or fatal infections. [1] | |

**Important potential risks**

| Risk | What is known |
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| Tumour Lysis Syndrome | The levels of uric acid (showing that the cancer cells are destroyed) in your blood (hyperuricaemia) may be high during treatment. Your doctor will tell you if you need to take any medicine to control this. [6] |

**Missing information**

| Risk | What is known |
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| Limited information on the use during pregnancy and lactation | Avoid becoming pregnant while the patient or her partner is being treated with Cytarabine. If sexually active, use effective birth control to prevent pregnancy during treatment, whether male or female. Cytarabine may cause birth defects, so it is important to tell your doctor if pregnant. Men and women have to use effective contraception during and up to 6 months after treatment.<br>Stop breast-feeding before starting treatment with Cytarabine because this medicine may be harmful to infants being breast-fed. Ask your doctor or pharmacist for advice before taking any medicine. [6] |
| Limited safety data for use in | Patient should stop breast-feeding before starting treatment with |

| Risk | What is known |
|---|---|
| infants | Cytarabine because this medicine may be harmful to infants being breast-fed. (6)<br>The safety of this drug for use in infants is not established. (1) |

### VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for cytarabine can be found in the cytarabine's EPAR.

This medicine has no additional risk minimisation measures.

### VI.2.6 Planned post authorisation development plan

No studies planned.

### VI.2.7 Summary of changes to the risk management plan over time

| Version | Date | Safety Concern | Comment |
|---|---|---|---|
| 2.0 | | Following safety concerns are included:<br>**Important identified risk**:<br>Bone marrow suppression (including leucopenia and | - |

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| | | thrombocytopenia)<br>Infections (including neutropenic sepsis)<br>**Important potential risk:**<br>Tumour Lysis Syndrome | |