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

Important identified risk (s)	• Myelosuppression • Increased susceptibility to infections • Tumour Lysis Syndrome • Central nerve system toxicity with high dose cytarabine • Pulmonary toxicity (Pulmonary oedema, adult respiratory distress syndrome) with high dose cytarabine • Gastrointestinal toxicity with high dose cytarabine • Hepatic toxicity with high dose cytarabine • Peripheral motor and sensory neuropathies with high dose cytarabine • Neurologic reactions (headache, paralysis, coma and stroke like episodes) – cytarabine in combination with methotrexate • Pancreatitis
Important potential risk (s)	None
Missing information	• Use in lactating women

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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
Important identified risk: Myelosuppression	Section 4.2, 4.3, 4.4, 4.8 and 4.9 of cytarabine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important identified risk: Increased susceptibility to infections	Section 4.4, 4.5 and 4.8 of cytarabine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important identified risk: Tumour Lysis	Section 4.4 and 4.8 of cytarabine Accord SmPC and corresponding sections of PIL have	None proposed

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Syndrome	information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	
Important identified risk: Central nerve system toxicity with high dose cytarabine	Section 4.3, 4.4, 4.8 and 4.9 of cytarabine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important identified risk: Pulmonary toxicity (Pulmonary oedema, adult respiratory distress syndrome) with high dose cytarabine	Section 4.4 and 4.8 of cytarabine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important identified risk: Gastrointestinal toxicity with high dose cytarabine	Section 4.4 and 4.8 of cytarabine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important identified risk: Hepatic toxicity with high dose cytarabine	Section 4.8 of cytarabine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures	None proposed

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	including the prescription only status of the product.	
Important identified risk: Peripheral motor and sensory neuropathies with high dose cytarabine	Section 4.4 of cytarabine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important identified risk: Neurologic reactions (headache, paralysis, coma and stroke like episodes) – cytarabine in combination with methotrexate	Section 4.4, 4.5 and 4.8 of cytarabine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important identified risk: Pancreatitis	Section 4.8 of cytarabine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing information: Use in lactating women	Section 4.6 of cytarabine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the	None proposed

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	product.	

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Acute myeloid leukaemia (AML):

Acute myeloid leukemia (AML) is a type of cancer characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells. As an acute leukemia, AML progresses rapidly and is typically fatal within weeks or months if left untreated. AML is the most common acute leukemia affecting adults, and its incidence increases with age. The number of new cases of acute myeloid leukemia in adults in Europe is 5–8 cases/100 000 population /year. Acute myeloid leukemia (AML) accounts for approximately 25% of all leukemias in adults in the Western world. Worldwide, the occurrence of AML is highest in the U.S., Australia, and Western Europe. The development of AML has been associated with several risk factors including 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.

Acute lymphocytic leukemia/ Acute lymphoblastic leukemia (ALL):

It is a type of white blood cell cancer and 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. Numbers 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. Common risk factors for ALL include genetic disorders and exposures

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to viruses as well as radiation, chemical, or other occupational hazards and previous chemotherapy.

Chronic myeloid leukemia (CML):

Chronic myelogenous leukemia is a type of blood cancer in which the bone marrow makes too many white blood cells. It accounts for 20% of all leukemias affecting adults. CML is one of the few cancers known to be caused by a single, specific genetic mutation. More than 90% of cases result from a cytogenetic aberration known as the Philadelphia chromosome. CML progresses through three phases: chronic, accelerated, and blast. In the blast phase, immature cells rapidly proliferate. Approximately 85% of patients are diagnosed in the chronic phase and then progress to the accelerated and blast phases after 3-5 years. CML accounts for 20% of all leukemias affecting adults. It typically affects middle-aged individuals. Younger patients may present with a more aggressive form of CML, such as in accelerated phase or blast crisis. Uncommonly, CML may appear as a disease of new onset in elderly individuals.

Leukaemic or lymphomatous meningitis:

Lymphoma is a group of blood cell tumors that develop from lymphocytes (a type of white blood cell). Non-Hodgkin lymphomas, which are defined as being all lymphomas except Hodgkin lymphoma, are more common than Hodgkin lymphoma. The incidence of non-Hodgkin lymphoma increases with age. It is further divided into several subtypes. About 90% of lymphomas are non-Hodgkin lymphomas. Risk factors for common types of non-Hodgkin lymphomas include autoimmune diseases, HIV/AIDS, infection. The five-year survival rate in the United States non-Hodgkin lymphomas is 69%. Worldwide, lymphomas developed in 566,000 people in 2012 and caused 305,000 deaths. They make up 3–4% of all cancers, making them as a group the seventh-most common form. In children, they are the third-most common cancer. Treatment may involve one or more of the following: chemotherapy, radiation therapy, targeted therapy, and surgery.

Meningeal neoplasms:

In meningeal leukemia, cancer cells have spread from the original (primary) tumor to the

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meninges (thin layers of tissue that cover and protect the brain and spinal cord). The cancer may cause the meninges to be inflamed. Many individuals have meningiomas, but remain asymptomatic, so the meningiomas are discovered during an autopsy. In the 1970s, tumors causing symptoms were discovered in 2 out of 100,000 people, while tumors discovered without causing symptoms occurred in 5.7 out of 100,000, for a total incidence of 7.7/100,000. With the advent of modern sophisticated imaging systems such as CT scans, the discovery of asymptomatic meningiomas has tripled. Meningiomas are more likely to appear in women than men, though when they appear in men, they are more likely to be malignant. Meningiomas may appear at any age, but most commonly are noticed in men and women age 50 or older, with meningiomas becoming more likely with age.

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
Disease related to blood counts (Myelosuppression)	Cytarabine strongly reduces blood cell production in the bone marrow. This can make you more prone to infections or bleeding. The blood cell	Do not take cytarabine if your blood cell count (number of cells in your blood) is very low due to some cause other than cancer

Risk	What is known	Preventability
	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.	(unless your doctor decides the benefits of treatment outweigh the risks) Take special care with Cytarabine if your blood cell count is low. Your doctor will monitor your blood to check your blood cell count.
Risk of infection in people with low number of neutrophils cells (Increased susceptibility to infections)	Cytarabine strongly reduces blood cell production in the bone marrow. This can make you more prone to infections or bleeding. Possible side effects: Common: Not enough white and red blood cells or blood platelets, which may make you more prone to infections or bleeding. Others: • Blood infection (sepsis) • Viral, bacterial etc infections Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cytarabine, may result in serious or	Testing blood regularly and examine bone marrow if required. 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.

Risk	What is known	Preventability
	fatal infections.	
A group of metabolic complications that can occur after treatment of cancer (Tumour Lysis Syndrome)	The levels of uric acid (showing that the cancer cells are destroyed) in your blood (hyperuricaemia) may be high during treatment.	Do not take cytarabine if your uric acid in your blood is very high. Take special care with Cytarabine if your uric acid in your blood is too high. Your doctor will monitor your uric acid in your blood.
Central nervous system toxicity with high dose cytarabine	Severe and at times fatal central nervous system (CNS) toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following some experimental cytarabine dose schedule. People taking cytarabine may experience neuritis or neural toxicity and pain, neurotoxicity rash with unknown frequency.	Take special care with cytarabine if serious and sometimes life-threatening side effects can occur in the central nervous system when treated with high doses of cytarabine.
Pulmonary toxicity (Pulmonary oedema, adult respiratory distress syndrome) with high dose cytarabine	People taking cytarabine may uncommonly (may affect up to 1 in every 100 people) experience lung infection. Severe and at times fatal side effects on the lungs such as fluid in the lungs (different from that seen with	Take special care with cytarabine if serious and sometimes life-threatening side effects can occur in the lungs when treated with high doses of cytarabine.

Risk	What is known	Preventability
	conventional therapy regimens of cytarabine) have been reported after using experimental dose schedules.	
Gastrointestinal toxicity with high dose cytarabine	Severe and at times fatal gastrointestinal (GI) toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following some experimental cytarabine dose schedule. People taking cytarabine may experience gastrointestinal haemorrhage (black tarry stools which may indicate bleeding in the digestive system) with unknown frequency.	The side effects on the digestive tract are less if cytarabine is given by infusion. Take special care with cytarabine if serious and sometimes life-threatening side effects can occur in the bowels when treated with high doses of cytarabine.
Liver (Hepatic) toxicity with high dose cytarabine	Severe and at times fatal side effects on liver such as severe liver abscess or enlargement have been reported after using experimental dose schedules. People taking cytarabine may very commonly (may affect more than 1 people in 10) experience impaired liver function. People taking cytarabine may commonly (may affect more than 1	Your doctor will monitor your liver functions during treatment with cytarabine.

Risk	What is known	Preventability
	people in 10, but less than 1 people in 100) experience reversible effects on the liver such as increased enzyme levels. People taking cytarabine experience impaired liver function with unknown frequency.	
Peripheral motor and sensory neuropathies (damage to or disease affecting nerves) with high dose cytarabine	Patient experienced peripheral motor and sensory neuropathies (damage to or disease affecting nerves) after consolidation with high doses of cytarabine. People taking cytarabine may uncommonly (may affect up to 1 in every 100 people) experience peripheral neuropathy (damage to or disease affecting nerves) and paraplegia (paralysis of the legs and lower body, typically caused by spinal injury or disease) at intrathecal administration. Severe and at times fatal side effects on nervous system have been reported after using experimental dose schedules.	Patients treated with high doses of cytarabine should be observed for neuropathy since dose adjustments may be needed to avoid irreversible neurologic disorders.
Severe effects on your brain	There is evidence of pharmacodynamic interaction	Do not use cytarabine if you have had severe effects on your brain

Risk	What is known	Preventability
(headache, paralysis, coma and stroke like episodes) (Neurologic reactions – cytarabine in combination with methotrexate)	between methotrexate and cytarabine leading to severe effects on your brain (encephalopathy). Effectiveness of the methotrexate may be reduced or increased by cytarabine.	(encephalopathy) after treatment with methotrexate. Please tell your doctor if you are taking or have recently taken methotraxate obtained without a prescription.
Inflammation of the pancreas (Pancreatitis)	People taking cytarabine may very rarely (may affect more than 1 person in 10,000) experience inflammation of the pancreas. Patient also experienced inflammation of the pancreas after high dose cytarabine treatment.	If you experienced severe pain in the abdomen (this may be a symptom of inflammation of the pancreas) tell your doctor or nursing staff immediately.

Important potential risks

Risk	What is known
None	Not applicable

Missing information

Risk	What is known
Use in lactating women	Stop breast-feeding before starting treatment with cytarabine because this medicine may be harmful to infants being breast-

Risk	What is known
	fed. Ask your doctor or pharmacist for advice before taking any medicine. Patient should stop breast-feeding before starting treatment with cytarabine because this medicine may be harmful to infants being breast-fed. The safety of this drug for use in infants is not established.

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

Not applicable

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