ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vyxeos 44 mg/100 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 44 mg of daunorubicin and 100 mg of cytarabine.

After reconstitution the solution contains 2.2 mg/mL daunorubicin and 5 mg/mL cytarabine encapsulated in liposomes in a fixed combination in a 1:5 molar ratio.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

Purple, lyophilised cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vyxeos is indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

4.2 Posology and method of administration

Vyxeos treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products.

Vyxeos has a different posology than daunorubicin injection and cytarabine injection and it must not be interchanged with other daunorubicin and/or cytarabine containing products (see section 4.4).

Posology
Vyxeos dosing is based on the patient's body surface area (BSA) according to the following schedule:

Therapy	Dosing schedule
First induction	daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 on days 1, 3, and 5
Second induction	daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 on days 1 and 3
Consolidation	daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 on days 1 and 3

Recommended dosing schedule for induction of remission
The recommended dosing schedule of Vyxeos 44 mg/100 mg/m^2, administered intravenously over 90 minutes:

- on days 1, 3, and 5 as the first course of induction therapy.
- on days 1 and 3 as subsequent course of induction therapy, if needed.

A subsequent course of induction may be administered in patients who do not show disease progression or unacceptable toxicity. The attainment of a normal-appearing bone marrow may require more than one induction course. Evaluation of the bone marrow following recovery from the previous course of induction therapy determines whether a further course of induction is required. Treatment should be continued as long as the patient continues to benefit or until disease progression up to maximum of 2 induction courses.

Recommended dosing schedule for consolidation
The first consolidation cycle should be administered 5 to 8 weeks after the start of the last induction.

The recommended dosing schedule of Vyxeos is 29 mg/65 mg/m^2, administered intravenously over 90 minutes:

- on days 1 and 3 as subsequent courses of consolidation therapy, if needed.

Consolidation therapy is recommended for patients achieving remission who have recovered to absolute neutrophil count (ANC) > 500/µL and the platelet count has recovered to greater than 50,000/µL in the absence of unacceptable toxicity. A subsequent course of consolidation may be administered in patients who do not show disease progression or unacceptable toxicity within the range of 5 to 8 weeks after the start of the first consolidation. Treatment should be continued as long as the patient continues to benefit or until disease progression, up to maximum of 2 consolidation courses.

Recommended dose adjustments during treatment
Patients should be monitored for haematologic response and toxicities.

Dosing should be delayed or permanently discontinued, if necessary, as described below.

Patients may be pre-medicated for nausea and vomiting. An anti-hyperuricemic therapy should be considered (e.g., allopurinol) prior to initiating Vyxeos.

Hypersensitivity

For mild hypersensitivity symptoms (e.g., mild flushing, rash, pruritus), the treatment should be stopped, and the patient should be supervised, including monitoring of vital signs. The treatment should be restarted slowly once the symptoms have resolved, by halving the rate of infusion and intravenous diphenhydramine (20-25 mg) and intravenous dexamethasone (10 mg) should be given.

For moderate hypersensitivity symptoms (e.g., moderate rash, flushing, mild dyspnoea, chest discomfort) the treatment should be stopped. Intravenous diphenhydramine (20-25 mg or equivalent) and intravenous dexamethasone (10 mg) should be given. The infusion should not be restarted. When the patient is retreated, Vyxeos should be given at the same dose and rate and with premedication.

For severe/life-threatening hypersensitivity symptoms (e.g., hypotension requiring vasopressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalised urticaria), the treatment should be stopped. Intravenous diphenhydramine (20-25 mg) and dexamethasone (10 mg) should be given, and an epinephrine (adrenaline) or bronchodilators should be added if indicated. Do not reinitiate infusion, and do not retreat. Treatment with Vyxeos should be permanently discontinued. Patients should be monitored until symptoms resolve (see sections 4.4 and 4.8).

Missed dose
If a planned dose of Vyxeos is missed, the dose should be administered as soon as possible and the dosing schedule adjusted accordingly, maintaining the treatment interval.

Cardiotoxicity
Assessment of cardiac function prior to start of treatment is recommended, especially in patients with a high risk of cardiac toxicity. Vyxeos treatment should be discountinued in patients who develop signs or symptoms of cardiomyopathy, unless the benefits outweigh the risks (see section 4.4).

Special populations

Renal impairment
Dose adjustment is not required for patients with mild (creatinine clearance [CrCL] 60 mL/min to 89 mL/min by Cockcroft Gault equation [C-G]) or moderate (CrCL 30 mL/min to 59 mL/min) renal impairment. There is no experience with Vyxeos in patients with severe renal impairment (CrCL 15 mL/min to 29 mL/min) or end-stage renal disease. Vyxeos should only be used in patients with severe renal impairment if the benefits outweigh the risks (see sections 4.4 and 5.2).

Hepatic impairment
Dose adjustment is not required for patients with a bilirubin level less than or equal to 50 µmol/L. There is no experience with Vyxeos in patients with hepatic impairment resulting in a bilirubin level greater than 50 µmol/L. Vyxeos should only be used in patients with severe hepatic impairment if the benefits outweigh the risks (see section 4.4).

Elderly population
No dose adjustment is required in elderly patients (≥65 years) (see section 5.2).
Paediatric population
The safety and efficacy of Vyxeos in children aged 0-18 years have not yet been established. No data are available.

Method of administration
Vyxeos is for intravenous use only. It must not be administered via an intramuscular, intrathecal, or subcutaneous route.

Vyxeos is administered by intravenous infusion over a period of 90 minutes. Care should be taken to ensure there is no extravasation to prevent the risk of tissue necrosis.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

History of serious hypersensitivity to the active substances or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Other daunorubicin and/or cytarabine-containing products
Vyxeos must not be substituted or interchanged with other daunorubicin and/or cytarabine containing products. Due to substantial differences in the pharmacokinetic parameters, the dose and schedule recommendations for Vyxeos are different from those for daunorubicin hydrochloride injection, cytarabine injection, daunorubicin citrate liposome injection, and cytarabine liposome injection. The medicinal product name and dose should be verified prior to administration to avoid dosing errors.

Severe myelosuppression
Severe myelosuppression (including fatal infections and haemorrhagic events) has been reported in patients after administration of a therapeutic dose of Vyxeos. Serious or fatal haemorrhagic events, including fatal central nervous system (CNS) haemorrhages, associated with severe thrombocytopenia,

have occurred in patients treated with Vyxeos. Baseline assessment of blood counts should be obtained, and patients should be carefully monitored during treatment with Vyxeos for possible clinical complications due to myelosuppression. Due to the long plasma half-life of Vyxeos, time to recovery of ANC and platelets may be prolonged and require additional monitoring.

Prophylactic anti-infectives (including anti-bacterial, anti-virals, anti-fungals) may be administered during the period of profound neutropenia until ANC returns to 500/μL or greater. If myelosuppressive complications occur, appropriate supportive measures should be used, e.g., anti-infectives, colony-stimulating factors, transfusions. Blood counts should be regularly monitored until recovery (see section 4.8).

Cardiotoxicity

Cardiotoxicity is a known risk of anthracycline treatment. Prior therapy with anthracyclines (including patients who have previously received the recommended maximum cumulative doses of doxorubicin or daunorubicin hydrochloride), pre-existing cardiac disease (including impaired cardiac function), previous radiotherapy of the mediastinum, or concomitant use of cardiotoxic products may increase the risk of daunorubicin-induced cardiac toxicity.

Total cumulative doses of non-liposomal daunorubicin greater than 550 mg/m^2 have been associated with an increased incidence of treatment-induced congestive heart failure. This limit appears lower (400 mg/m^2) in patients who received radiation therapy to the mediastinum. The relationship between cumulative Vyxeos dose and the risk of cardiac toxicity has not been determined. Total cumulative exposure of daunorubicin has been described in the table below.

Table 1: Cumulative exposure of daunorubicin per course of Vyxeos

Therapy	Daunorubicin per dose	Number of doses per course	Daunorubicin per course
First induction	44 mg/m^2	3	132 mg/m^2
Second induction	44 mg/m^2	2	88 mg/m^2
Each consolidation	29 mg/m^2	2	58 mg/m^2

A baseline cardiac evaluation with an electrocardiogram (ECG) and a multi-gated radionuclide angiography (MUGA) scan or an echocardiography (ECHO) is recommended, especially in patients with risk factors for increased cardiac toxicity. Cardiac function should be closely monitored.

Treatment with Vyxeos should be discontinued in patients with impaired cardiac function unless the benefit of initiating or continuing treatment outweighs the risk (see sections 4.5 and 4.8).

Pregnancy warning/women of childbearing potential

Patients should be advised to avoid becoming pregnant while receiving Vyxeos. Male patients and women of childbearing potential must use an effective method of contraception during treatment and for 6 months following the last dose of Vyxeos (see section 4.6).

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine.

For moderate hypersensitivity symptoms (e.g., moderate rash, flushing, mild dyspnoea, chest discomfort) the treatment should be stopped. Intravenous diphenhydramine (20-25 mg or equivalent) and intravenous dexamethasone (10 mg) should be given. The infusion should not be restarted. When the patient is retreated, Vyxeos should be given at the same dose and rate and with premedication.

For severe/life-threatening hypersensitivity symptoms (e.g., hypotension requiring vasopressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalised urticaria), the

treatment should be stopped. Intravenous diphenhydramine (20-25 mg) and dexamethasone (10 mg) should be given, and an epinephrine (adrenaline) or bronchodilators should be added if indicated. Do not reinitiate infusion, and do not retreat. Treatment with Vyxeos should be permanently discontinued. Patients should be monitored until symptoms resolve (see sections 4.2 and 4.8).

Tissue necrosis
Daunorubicin has been associated with local tissue necrosis at the site of medicinal product extravasation. In clinical studies with Vyxeos, one event of extravasation occurred, but no necrosis was observed. Care should be taken to ensure that there is no extravasation of medicinal product when Vyxeos is administered. Vyxeos should be administered intravenously only. Do not administer via an intramuscular, intrathecal, or subcutaneous route (see section 4.2).

Evaluation of hepatic and renal function
Hepatic or renal impairment may increase the risk of toxicity associated with daunorubicin and cytarabine. Evaluation of hepatic and renal function using conventional clinical laboratory tests is recommended prior to administration of Vyxeos and periodically during treatment. There is no experience with Vyxeos in patients with baseline serum bilirubin greater than 50 µmol/L, severe renal impairment (creatinine clearance less than 30 mL/min), or end stage renal disease. Vyxeos should only be used in patients with severe hepatic and/or renal impairment if the benefits outweigh the risks (see section 4.2).

Laboratory tests
Vyxeos may induce hyperuricemia secondary to rapid lysis of leukaemic cells. Blood uric acid levels should be monitored and appropriate therapy initiated in the event that hyperuricemia develops.

History of Wilson’s disease or other copper-related disorder
Each vial contains 100 mg of copper gluconate, which corresponds to 14 mg of elemental copper. Vyxeos should only be used in patients with a history of Wilson’s disease or other copper-related disorder if the benefits outweigh the risks (see section 6.1). Discontinue Vyxeos in patients with signs or symptoms of acute copper toxicity.

Immunosuppressant effects/Increased susceptibility to infections
Administration of live or live-attenuated vaccines in patients that are immunocompromised by chemotherapeutic agents may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving Vyxeos. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Gastrointestinal mucositis and diarrhoea
It should be taken into consideration that the absorption of oral accompanying medicinal products may be considerably influenced by gastrointestinal mucositis and/or diarrhoea frequently occurring in association with intensive chemotherapy.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Vyxeos. The delivery of daunorubicin and cytarabine in the Vyxeos liposomal formulation is anticipated to reduce the possibility of interactions, because systemic free-drug concentrations of daunorubicin and cytarabine are much lower than when administered as the non-liposomal formulation.

Cardiotoxic agents
Concurrent use of cardiotoxic agents may increase the risk of cardiotoxicity. Use of Vyxeos in patients who have previously received doxorubicin increases the risk of cardiotoxicity (see section 4.4). Do not administer Vyxeos in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored.

Hepatotoxic agents
Hepatotoxic medicinal products may impair liver function and increase the toxicity. Since daunorubicin is metabolised by the liver, changes in hepatic function induced by concomitant therapies may affect metabolism, pharmacokinetics, therapeutic efficacy, and/or the toxicity of Vyxeos (see section 5.2). Hepatic function should be monitored more frequently when Vyxeos is coadministered with hepatoxic agents.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Women of childbearing potential should avoid becoming pregnant while receiving Vyxeos. Women of childbearing potential should use effective contraception while they or their male partner undergo treatment. Women of childbearing potential should not receive treatment until pregnancy is excluded.

Women of childbearing potential should undergo pregnancy testing before initiation of Vyxeos. Men with sexual partners of reproductive potential and women should use effective contraception during treatment and for 6 months following the last dose of Vyxeos.

Pregnancy
There are no data on the use of Vyxeos in pregnant women. Based on results from animal studies and its mechanism of action, Vyxeos should not be used during pregnancy, unless the clinical condition of the woman requires treatment and justifies the potential risk to the foetus (see section 5.3).

If the medicinal product is used during pregnancy, or if the patient becomes pregnant while receiving Vyxeos, the woman should be informed of the potential hazard to the foetus. In any case, cardiologic examination and a blood count are recommended in foetuses and newborns born to mothers who received treatment during pregnancy.

Breast-feeding
It is not known whether Vyxeos is excreted in human milk. Because of the potential for serious adverse reactions in breast-feeding children from Vyxeos, mothers should be advised to discontinue breast-feeding during Vyxeos therapy.

Fertility
Based on findings in animals, male fertility may be compromised by treatment with Vyxeos (see section 5.3).

4.7 Effects on ability to drive and use machines

Vyxeos has minor influence on the ability to drive and use machines. Fatigue and dizziness have been reported with the use of Vyxeos. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently occurring adverse reactions (ADRs) were hypersensitivity including rash (66.9%), febrile neutropenia (63.5%), oedema (52.3%), diarrhoea/colitis (49.9%), mucositis (49.9%), fatigue (46.4%), musculoskeletal pain (44.5%), abdominal pain (36.3%), decreased appetite (33.9%), cough (33.9%), headache (32.3%), chills (31.2%), arrhythmia (30.4%), pyrexia (29.6%), sleep disorders (25.1%), and hypotension (23.7%).

The most serious and frequently occurring ADRs were infection (58.7%), cardiotoxicity (18.7%) and haemorrhage (13.1%).

Tabulated list of adverse reactions
ADRs have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical studies.

Frequencies are defined as: 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); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. For classification of ADRs which occur at Grades 3-5, a comprehensive listing is available from the NCI at NCI CTCAE. Toxicity is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), with specific parameters according to the organ system involved. Death (Grade 5) is used for some of the criteria to denote a fatality.

Table 2: ADRs reported in clinical studies in patients treated with Vyxeos (n=375)

System Organ Class	ADRs/Frequency (%)	Grade 3-5 ADRs/Frequency (%)
Infections and infestations	**Very Common** Infection (78.1)	**Very Common** Infection (58.7)
Blood and lymphatic system disorders	**Very Common** Febrile neutropenia (63.5) **Common** Thrombocytopenia (4.5) Neutropenia (3.7) Anaemia (3.2)	**Very Common** Febrile neutropenia (62.4) **Common** Thrombocytopenia (3.7) Neutropenia (3.5) Anaemia (2.1)
Immune systems disorders	**Very Common** Hypersensitivity (including rash) (66.9)	**Common** Hypersensitivity (including rash) (9.1)
Metabolism and nutrition disorders	**Common** Tumour lysis syndrome (7.5)	**Common** Tumour lysis syndrome (2.7)
Psychiatric disorders	**Very Common** Sleep disorders (25.1) Anxiety (17.3) Delirium (15.5)	**Common** Delirium (2.4) **Uncommon** Sleep disorders (0.5)
Nervous system disorders	**Very Common** Headache (32.3) Dizziness (23.2)	**Common** Headache (1.1) **Uncommon** Dizziness (0.8)
Eye disorders	**Very Common** Visual impairment (10.4)	**Uncommon** Visual impairment (0.3)
Cardiac disorders	**Very Common** Cardiotoxicity (72) Arrhythmia[a] (30.4) Chest pain (17.6)	**Very Common** Cardiotoxicity (18.7) **Common** Arrhythmia[a] (4.3) Chest pain (1.9)
Vascular disorders	**Very Common** Haemorrhage (69.1) Hypotension (23.7) Hypertension (17.3)	**Very Common** Haemorrhage (13.1) **Common** Hypertension (6.9) Hypotension (4.5)
Respiratory, thoracic and mediastinal disorders	**Very Common** Dyspnoea (36.5)	**Very Common** Dyspnoea (13.1)

System Organ Class	ADRs/Frequency (%)	Grade 3-5 ADRs/Frequency (%)
	Cough (33.9) Pleural effusion (13.9)	 **Uncommon** Pleural effusion (0.8)
Gastrointestinal disorders	**Very Common** Nausea (51.7) Diarrhoea/colitis (49.9) Mucositis (49.9) Constipation (42.7) Abdominal pain (36.3) Decreased appetite (33.9) Vomiting (27.7) **Common** Dyspepsia (9.6)	**Common** Diarrhoea/colitis (6.1) Abdominal pain (2.9) Mucositis (2.1) Decreased appetite (1.6) Constipation (1.1) Nausea (1.1) **Uncommon** Dyspepsia (0.5) Vomiting (0.3)
Skin and subcutaneous tissue disorders	**Very Common** Pruritus (17.3) Hyperhidrosis (10.1) **Common** Night sweats (8.3) Alopecia (3.2) **Uncommon** Palmar-plantar erythrodysaesthesia syndrome (0.8)	**Uncommon** Hyperhidrosis (0.3)
Musculoskeletal and connective tissue disorders	**Very Common** Musculoskeletal pain (44.5)	**Common** Musculoskeletal pain (5.1)
Renal and urinary disorders	**Very Common** Renal insufficiency (10.4)	**Common** Renal insufficiency (6.4)
General disorders and administration site conditions	**Very Common** Oedema (52.3) Fatigue (46.4) Chills (31.2) Pyrexia (29.6)	**Very Common** Fatigue (10.4) **Common** Pyrexia (3.2) Oedema (2.7) **Uncommon** Chills (0.3)

[a] Arrhythmia group terms includes atrial fibrillation, bradycardia, and the most commonly reported arrhythmia was tachycardia

Description of selected adverse reactions

Infections
Due to the neutropenia experienced with Vyxeos, infections of various types were very common ADRs. Pneumonia, sepsis and bacteriaemia were the most frequently seen serious infection ADRs in the clinical studies population. The incidence of infection events was 78.1%; the incidence of non-serious events of infections was 73.1%, the incidence of serious events of infections was 28.5%; the incidence of infections which led to discontinuation is 0.5%. The incidence of fatal infections was 6.9%. The fatal infections experienced were sepsis and pneumonia (see section 4.4).

Haemorrhage
Due to the thrombocytopenia experienced with Vyxeos a variety of haemorrhagic events were seen in clinical studies. The most common haemorrhagic event was epistaxis, and the majority of these were considered not serious (29.1%). The incidence of haemorrhage events is 69.1%; the incidence of non-

serious events of haemorrhage was 67.2 %; the incidence of serious events of haemorrhage is 5.6%; the incidence of haemorrhage which led to discontinuation is 0. The incidence of fatal haemorrhage was 2.1%. Serious or fatal haemorrhagic events, including fatal central nervous system (CNS) haemorrhages, associated with severe thrombocytopenia were seen in patients treated with Vyxeos (see section 4.4).

Cardiotoxicity
Cardiotoxicities were seen in Vyxeos clinical studies. The most frequently reported serious ADRs were decreased ejection fraction and congestive cardiac failure. Cardiotoxicity is a known risk of anthracycline treatment. The incidence of all cardiotoxicity events was 72.0%; the incidence of non-serious events of cardiotoxicity was 68.5 %; the incidence of serious events of cardiotoxicity was 9.1%; the incidence of cardiotoxicity which led to discontinuation is 0. 5%. Incidence of fatal cardiotoxicity events is 0.5%. Cardiac arrest was reported as a fatal event; the patient experienced thrombocytopenia and neutropenia which contributed to cardiac arrest (see section 4.4).

Hypersensitivity
Hypersensitivity reactions were very common ADRs in Vyxeos clinical studies. The most frequently reported hypersensitivity ADRs were rash and the majority of these were not serious (38.9%). The incidence of all hypersensitivity events was 66.9%; the incidence of non-serious events of hypersensitivity was 66.4 %, of which 38.9 % were rash; the incidence of serious events of hypersensitivity is 1.1%; the frequency of hypersensitivity which led to discontinuation is 0. The frequency of fatal hypersensitivity events was 0 (see section 4.4).

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

There is no specific experience in the management of overdose in patients. If overdose occurs, exacerbation of adverse reactions associated with Vyxeos are expected and supportive treatment (incuding anti-infectives, blood and platelet transfusions, colony-stimulating factors, and intensive care as needed) should be provided until the patient recovers. Observe the patient carefully over time for signs of cardiotoxicity and provide appropriate supportive therapy as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, combinations of antineoplastic agents, ATC code: L01XY01.

Mechanism of action
Vyxeos is a liposomal formulation of a fixed combination of daunorubicin and cytarabine in a 1:5 molar ratio. The 1:5 molar ratio has been shown *in vitro* and *in vivo* to maximise synergistic antitumour activity in AML.

Daunorubicin has antimitotic and cytotoxic activity, which is achieved by forming complexes with DNA, inhibiting topoisomerase II activity, inhibiting DNA polymerase activity, affecting regulation of gene expression, and producing DNA-damaging free radicals.

Cytarabine is a cell cycle phase-specific antineoplastic agent, affecting cells only during the S-phase of cell division. Intracellularly, cytarabine is converted into cytarabine-5-triphosphate (ara-CTP),

which is the active metabolite. The mechanism of action is not completely understood, but it appears that ara-CTP acts primarily through inhibition of DNA synthesis. Incorporation into DNA and RNA may also contribute to cytarabine cytotoxicity. Cytarabine is cytotoxic to proliferating mammalian cells in culture.

Vyxeos liposomes exhibit a prolonged plasma half-life following intravenous infusion, with greater than 99% of the daunorubicin and cytarabine in the plasma remaining encapsulated within the liposomes. Vyxeos delivers a synergistic combination of daunorubicin and cytarabine to leukaemia cells for a prolonged period of time. Based on data in animals, Vyxeos liposomes accumulate and persist in high concentration in the bone marrow, where they are preferentially taken up intact by leukaemia cells in an active engulfment process. In leukaemia-bearing mice, the liposomes are taken up by leukaemia cells to a greater extent than by normal bone marrow cells. After internalisation, Vyxeos liposomes undergo degradation, releasing daunorubicin and cytarabine within the intracellular environment, enabling the medicinal products to exert their synergistic antineoplastic activity.

Clinical efficacy and safety

The efficacy of Vyxeos in the treatment of high risk AML was evaluated in 1 controlled study.

Study 301 in patients with untreated high risk AML

Study 301 was a Phase 3 randomised, multicentre, open-label, parallel-arm, superiority study which evaluated Vyxeos vs. a standard combination of cytarabine and daunorubicin (7+3) in 309 patients between 60 to 75 years of age with untreated high risk AML. Patients with the following AML sub-types were included in the study: therapy-related AML (t-AML), myelodysplastic syndrome AML (MDS AML) and chronic myelomonocytic leukaemia AML (CMMoL AML) with documented history of MDS or CMMoL prior to transformation to AML, and *de novo* AML with karyotype changes characteristic of myelodysplasia, (per 2008 WHO criteria).

The study included 2 phases, 1) Treatment Phase during which patients received up to 2 induction and 2 consolidation courses, and 2) a Follow-up Phase, which began 30 days after the last induction or consolidation course and continued for up to 5 years from randomisation. The number of inductions and consolidations a patient received depended upon Complete Response (CR) or Complete Response with incomplete recovery (CRi), which was confirmed by bone marrow assessment. In clinical studies only, Vyxeos 100 units/m^2/day (equivalent to 44 mg/100 mg/m^2) was administered intravenously over 90 minutes on days 1, 3, and 5 for the first induction and on days 1 and 3 for patients requiring a second induction. A second induction was highly recommended for patients who did not achieve a CR or CRi in the first induction course and was mandatory for patients achieving greater than 50% reduction in percent blasts. Post-remission therapy with haematopoietic stem cell transplantation (HSCT) was permitted either in place of or after consolidation chemotherapy. For consolidation courses, in clinical studies only, the Vyxeos dose was reduced to 65 units/m^2/day (equivalent to 29mg/65 mg/m^2) on days 1 and 3. In the 7+3 arm, first induction consisted of cytarabine 100 mg/m^2/day on days 1 to 7 by continuous infusion, and daunorubicin 60 mg/m^2/day on days 1, 2, and 3 whereas second induction and consolidation cytarabine was dosed on days 1 to 5 and daunorubicin on days 1 and 2.

There were 153 patients randomised to Vyxeos and 156 patients randomised to the 7+3 control arm. The randomised patients had a median age of 68 (range 60-75 years), 61% were male, and 88% had an ECOG performance status of 0-1. At baseline 20% had t-AML, 54% had AML with an antecedent haematological disorder and 25% had *de novo* AML with myelodysplasia-related cytogenetic abnormalities; 34% had been treated previously with a hypomethylating agent for MDS;54% had an adverse karyotype.

The demographic and baseline disease characteristics were generally balanced between the study arms. FLT3 mutation was identified in 15% (43/279) of patients tested and NPM1 mutation was identified in 9% (25/283) patients tested.

The primary endpoint was overall survival measured from the date of randomisation to death from any cause. Vyxeos demonstrated superiority in overall survival in the ITT population compared with the comparator 7+3 treatment regimen (Figure 1). The median survival for the Vyxeos treatment group

was 9.56 months compared with 5.95 months for the 7+3 treatment group (Hazard Ratio = 0.69, 95% CI = 0.52, 0.90, two-sided log-rank test p = 0.005).

The overall rate of HSCT was 34% (52/153) in the Vyxeos arm and 25% (39/156) on the control arm.

Figure 1: Kaplan-Meier curve for overall survival, ITT population

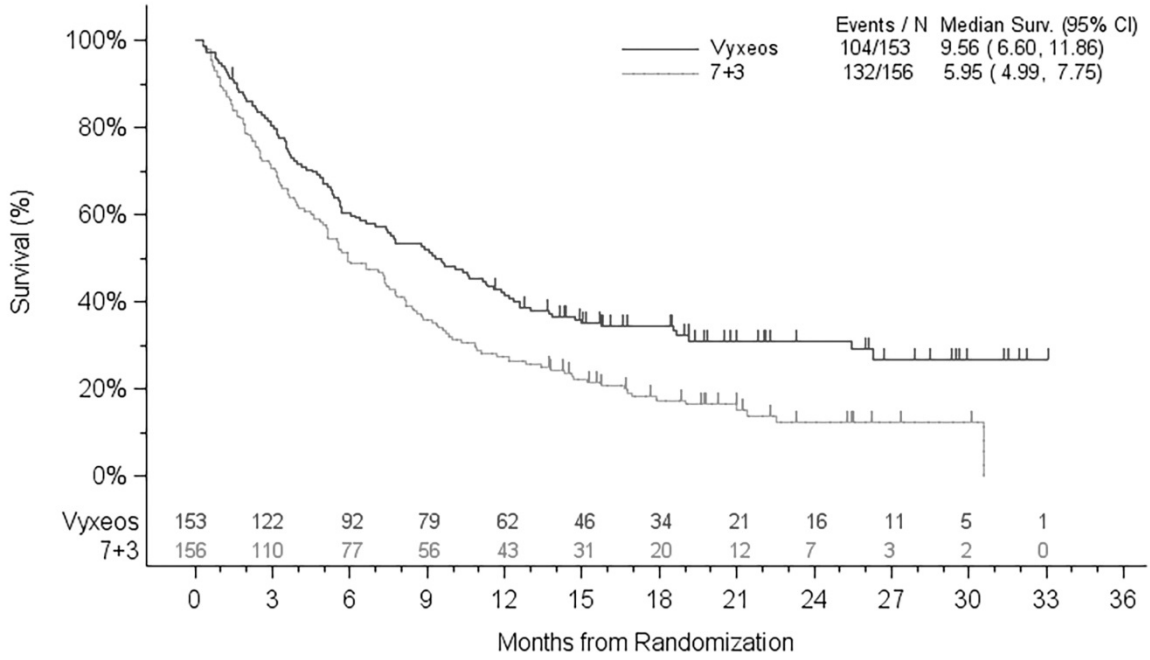

Table 4: Efficacy results for study 301

	Vyxeos N=153	**7+3 N=156**
Overall survival		
Median survival, months (95% CI)	9.56 (6.60, 11.86)	5.95 (4.99, 7.75)
Hazard ratio (95% CI)	0.69 (0.52, 0.90)	
p-value (2-sided) [a]	0.005	
Event free survival		
Median survival, months (95% CI)	2.53 (2.07, 4.99)	1.31 (1.08, 1.64)
Hazard ratio (95% CI)	0.74 (0.58, 0.96)	
p-value (2-sided) [a]	0.021	
Complete response rate		
CR, n (%)	57 (37)	40 (26)
Odds ratio (95% CI)	1.69 (1.03, 2.78)	
p-value (2-sided) [b]	0.040	
CR + CRi, n (%)	73 (48)	52 (33)
Odds ratio (95% CI)	1.77 (1.11, 2.81)	
p-value (2-sided) [b]	0.016	

Abbreviations: CI = Confidence interval; CR= Complete response; CRi= Complete response with incomplete recovery
[a] p-value from stratified log rank test stratifying by age and AML sub-type
[b] p-value from stratified Cochran-Mantel-Haenszel test stratified by age and AML sub-type

The European Medicines Agency has deferred the obligation to submit the results of studies with Vyxeos in one or more subsets of the paediatric population in AML (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of daunorubicin and cytarabine administered as Vyxeos were investigated in adult patients who received a dose of daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 administered as a 90-minute intravenous infusion on days 1, 3, and 5. The pharmacokinetics of each medicinal product was based on total plasma concentrations (i.e., encapsulated plus unencapsulated medicinal product). Following the dose administered on day 5, the mean (% coefficient of variation [CV]) maximum plasma concentrations (C_{max}) for daunorubicin was 26.0 (32.7%) mcg/mL and cytarabine was 62.2 (33.7%) mcg/mL. The mean (%CV) area under the curve (AUC) during one dosing interval for daunorubicin was 637 (38.4%) mcg.h/mL and cytarabine was 1900 (44.3%) mcg.h/mL.

When daunorubicin and cytarabine are administered as components of Vyxeos, the liposomes appear to govern their tissue distribution and rates of elimination; therefore, while the non-liposomal medicinal products have markedly different clearance (CL), volume of distribution (V), and terminal half-life ($t_{1/2}$) Vyxeos causes these pharmacokinetic parameters to converge.

The accumulation ratio was 1.3 for daunorubicin and 1.4 for cytarabine. There was no evidence of time-dependent kinetics or major departures from dose proportionality over the range of 1.3 mg/3 mg per m^2 to 59 mg/134 mg per m^2 (0.03 to 1.3 times the approved recommended dosage).

Distribution
The volume of distribution (%CV) for daunorubicin is 6.6 L (36.8%) and cytarabine is 7.1 L (49.2%). Plasma protein binding was not evaluated.

Metabolism and biotransformation
Similar to non-liposomal daunorubicin and cytarabine, subsequent to release from Vyxeos liposomes, both daunorubicin and cytarabine are extensively metabolised in the body. Daunorubicin is mostly catalysed by hepatic and non-hepatic aldo-keto reductase and carbonyl reductase to the active metabolite daunorubicinol. Cytarabine is metabolised by cytidine deaminase to the inactive metabolite 1-β (beta)-D-arabinofuranosyluracil (AraU). Unlike non-liposomal daunorubicin and cytarabine, which are quickly metabolised to the respective metabolites, daunorubicin and cytarabine after Vyxeos administration are free bases encapsulated in liposomes. Plasma concentration-time profiles obtained from 13 to 26 patients who received Vyxeos 100 units/m^2 (equivalent to 44 mg/ m^2 of daunorubicin and 100 mg/m^2 of cytarabine).on days 1, 3, and 5 show the mean AUC_{last} metabolite:parent ratio for daunorubicinol and AraU were 1.79% and 3.22% to that for daunorubicin and cytarabine, respectively; which are lower than those typically reported for non-liposomal products, ~40-60% for daunorubicinol:daunorubicin and ~80% for AraU:cytarabine. The lower percentages of metabolite:parent ratios after Vyxeos administration indicate that most of the total daunorubicin and cytarabine in the circulation is trapped inside the Vyxeos liposomes, where they are inaccessible to medicinal product-metabolising enzymes.

Elimination
Vyxeos exhibits a prolonged half-life (%CV) of 31.5 h (28.5%) for daunorubicin and 40.4 h (24.2%) for cytarabine with greater than 99% of the daunorubicin and cytarabine in the plasma remaining encapsulated within the liposomes. The clearance (%CV) is 0.16 L/h (53.3%) for daunorubicin and 0.13 L/h (60.2%) for cytarabine.

Urinary excretion of daunorubicin and daunorubicinol accounts for 9% of the administered dose of daunorubicin, and urinary excretion of cytarabine and AraU accounts for 71% of the administered dose of cytarabine.

Special populations
Age, sex, race, body weight, body mass index, and white blood cell count do not have a clinically important effect on the exposure of total daunorubicin or cytarabine after adjusting dose by body surface area.

Paediatric population
Insufficient pharmacokinetic data were collected in paediatric patients to draw conclusions.

Elderly population
The pharmacokinetics of Vyxeos in patients aged > 85 years has not yet been evaluated. No data are available.

Hepatic impairment
The pharmacokinetics of total daunorubicin and cytarabine were not altered in patients with bilirubin ≤ 50 µmol/L. The pharmacokinetics in patients with bilirubin greater than 50 µmol/L is unknown.

Renal impairment
Based on a population pharmacokinetic analysis using data from clinical studies in patients, no significant difference in clearance of daunorubicin or cytarabine was observed in patients with pre-existing mild to moderate renal impairment (60 mL/min ≥ to ≤ 89 mL/min creatinine clearance [CrCL] for mild, and 30 mL/min ≥ to ≤ 59 mL/min creatinine clearance [CrCL] for moderate) compared to patients with baseline normal renal function (CrCL ≥ 90 mL/min). The potential effects of severe renal impairment (CrCL 15 mL/min ≥ to ≤ 29 mL/min, C-G) and end-stage renal disease on the pharmacokinetics of daunorubicin and cytarabine administered as Vyxeos are unknown (see section 4.2).

5.3 Preclinical safety data

Repeat-dose toxicity of Vyxeos was tested in two-cycle intravenous infusion toxicity studies with 28-day recovery periods conducted in rats and dogs. Adverse effects of Vyxeos occurred at all tested dose levels (low to null safety margins as based on systemic exposures) and were generally consistent with those known for non-liposomal daunorubicin and/or cytarabine, comprising mainly findings of gastrointestinal and hematological toxicity. Although central nervous system (CNS) and cardiovascular system parameters were included in these studies, given the observed morbidity and mortality, there was insufficient information to arrive at an integrated assessment of safety pharmacology of Vyxeos. Vyxeos contains daunorubicin, which is known for its profound cardiotoxicity potential, and cytarabine, which is known to be associated with CNS toxicities.

Carcinogenicity, mutagenicity, and reproductive toxicity studies have not been conducted with Vyxeos.

While cytarabine is not a carcinogen, daunorubicin is a possible carcinogen, hence, Vyxeos may be associated with a carcinogenic potential. Both daunorubicin and cytarabine are genotoxic, therefore, Vyxeos may be associated with a genotoxic risk.

A high incidence of mammary tumours was observed about 120 days after a single intravenous dose of daunorubicin in rats (at about 1.7 times the human dose on a mg/m^2 basis). Daunorubicin was mutagenic in *in vitro* tests (Ames assay, V79 hamster cell assay), and clastogenic *in vitro* (CCRF-CEM human lymphoblasts) and *in vivo* (SCE assay in mouse bone marrow) tests.

Cytarabine was mutagenic in *in vitro* tests and was clastogenic *in vitro* (chromosome aberrations and SCE in human leukocytes) and *in vivo* (chromosome aberrations and SCE assay in rodent bone

marrow, mouse micronucleus assay). Cytarabine caused the transformation of hamster embryo cells and rat H43 cells *in vitro*.

Cytarabine was clastogenic to meiotic cells.

Both cytarabine and daunorubicin, tested separately, showed teratogenic and embryotoxic effects in animal studies. Furthermore, daunorubicin caused testicular atrophy and total aplasia of spermatocytes in the seminiferous tubules in dogs and cytarabine, sperm-head abnormalities in mice. A single dose of cytarabine in rats, administered on day 14 of gestation, reduced prenatal and postnatal brain size and caused permanent impairment of learning ability.

Environmental Risk Assessment (ERA)
Environmental risk assessment has shown that Vyxeos is not anticipated to have the potential to be persistent, bioaccumulative, or toxic to the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Distearoylphosphatidylcholine
Distearoylphosphatidylglycerol
Cholesterol
Copper gluconate
Trolamine (for pH adjustment)
Sucrose

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials
2 years.

Stability of reconstituted suspension in the vial
Chemical and physical in-use stability has been demonstrated for 4 hours at 2°C to 8°C when kept in an upright position.
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

Stability of diluted infusion solution
Chemical and physical in-use stability has been demonstrated for 4 hours at 2°C to 8°C.
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Keep the vial in the original carton in order to protect from light. Store in an upright position.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

50 mL vial (type 1 glass) with a stopper (chlorobutyl rubber), and an overseal (aluminium) containing 44 mg daunorubicin and 100 mg cytarabine.

Each pack contains either 1 vial, 2 vials or 5 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Vyxeos is a cytotoxic medicinal product. Applicable special handling and disposal procedures should be followed. The product is intended for single use only. Any unused product should be disposed of in accordance with local requirements for cytotoxic agents.

Preparation instructions

- Determine the dose and number of vials of Vyxeos based on the individual patient's BSA as outlined in section 4.2.
- Remove the appropriate number of vials of Vyxeos from the refrigerator and equilibrate to the room temperature (15°C to 30°C) for 30 minutes.
- Then, reconstitute each vial with 19 mL of sterile water for injections using a 20 mL syringe, and immediately thereafter start a 5-minute timer.
- Carefully swirl the contents of the vial for 5 minutes while gently inverting the vial every 30 seconds.
- Do not heat, vortex, or shake vigorously.
- After reconstitution, let it rest for 15 minutes.
- The reconstituted product should be an opaque, purple, homogeneous dispersion, essentially free from visual particulates.
- If the reconstituted product is not diluted into an infusion bag immediately, store in a refrigerator (2ºC to 8ºC) for up to 4 hours.
- Calculate the volume of reconstituted Vyxeos required using the following formula: [volume required (mL) = dose of daunorubicin (mg/m^2) x patient's BSA (m^2)/2.2 (mg/mL)]. The concentration of the reconstituted solution is 44 mg/20 mL (2.2 mg/mL) daunorubicin and 100 mg/20 mL (5 mg/mL) cytarabine.
- Gently invert each vial 5 times prior to withdrawing the concentrate for dilution.
- Aseptically withdraw the calculated volume of reconstituted Vyxeos from the vial(s) with a sterile syringe and transfer it to an infusion bag containing 500 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, or 5% glucose. There may be residual product remaining in the vial. Discard unused portion.
- Gently invert the bag to mix the solution. The dilution of the reconstituted product results in a deep purple, translucent, homogeneous dispersion.
- If the diluted infusion solution is not used immediately, store in a refrigerator (2°C to 8°C) for up to 4 hours.
- Gently invert the bag to mix the solution after refrigeration.

Administration instructions

- Do not mix Vyxeos with, or administer as an infusion with, other medicinal products.
- Administer Vyxeos by constant intravenous infusion over 90 minutes via an infusion pump through a central venous catheter or a peripherally inserted central catheter. **Do not use an in-line filter**.
- Flush the line after administration with sodium chloride 9 mg/mL (0.9%) solution for injection.

This medicinal product could have potential risk for the environment due to the cytotoxic and antimitotic activities, which could induce possible reproductive effects. All materials used for dilution and administration should be disposed of according to local procedures applicable to the discarding of antineoplastic agents. Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1308/001 1 vial
EU/1/18/1308/002 2 vials
EU/1/18/1308/003 5 vials

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2018

10. DATE OF REVISION OF THE TEXT

08/2018

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu