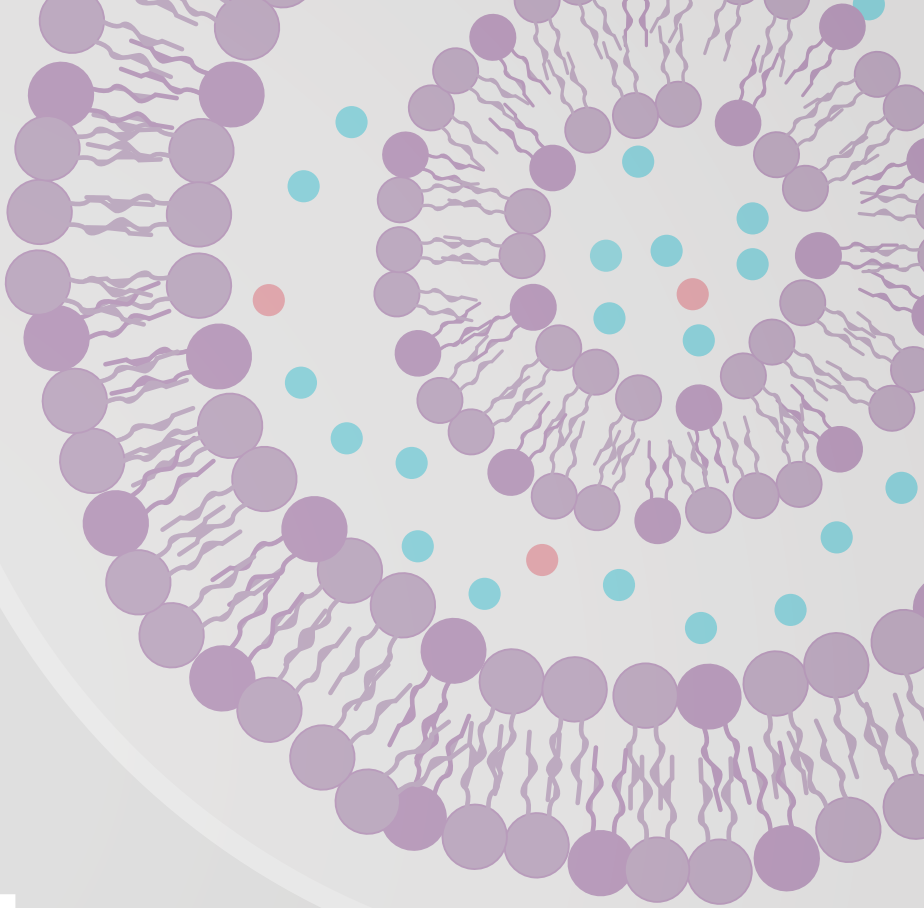

PHARMACIST INFORMATION

Prescribing information and adverse event reporting details can be found on page 13 of this booklet

Vyxeos® Liposomal

44 mg/100 mg Powder for concentrate for solution for infusion

daunorubicin / cytarabine

TOGETHER

First dual-drug advanced liposomal formulation of daunorubicin and cytarabine[1]

LONGER

Superior overall survival vs conventional chemotherapy* in adults with newly-diagnosed t-AML or AML-MRC[2]

LAYING THE FOUNDATION

TOWARDS LONG-TERM SURVIVAL IN HIGH-RISK¶ AML

INDICATION

Vyxeos Liposomal 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)[3]

* Comparator arm conventional chemotherapy is 7+3 in induction, 5+2 in second induction and consolidation where given
¶ High-risk AML defined as newly diagnosed t-AML or AML-MRC

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VYXEOS LIPOSOMAL HAS BEEN SPECIFICALLY DEVELOPED TO CONTROL THE DELIVERY OF DAUNORUBICIN AND CYTARABINE TO OPTIMISE EFFICACY OF TREATMENT

1+1 >2

- Drug combinations may act synergistically, additively or antagonistically depending on the molar ratio[1]
- Efficacy can be enhanced by ensuring each drug is delivered at a **synergistic** ratio[1]

In AML:

- **1:5 molar ratio** of daunorubicin and cytarabine has been shown to have a synergistic effect and increase anti-tumour activity in vitro[2]
- The differing pharmacokinetics of the individual drugs make it challenging to consistently deliver the synergistic molar ratio when administered as a free drug[4-7]

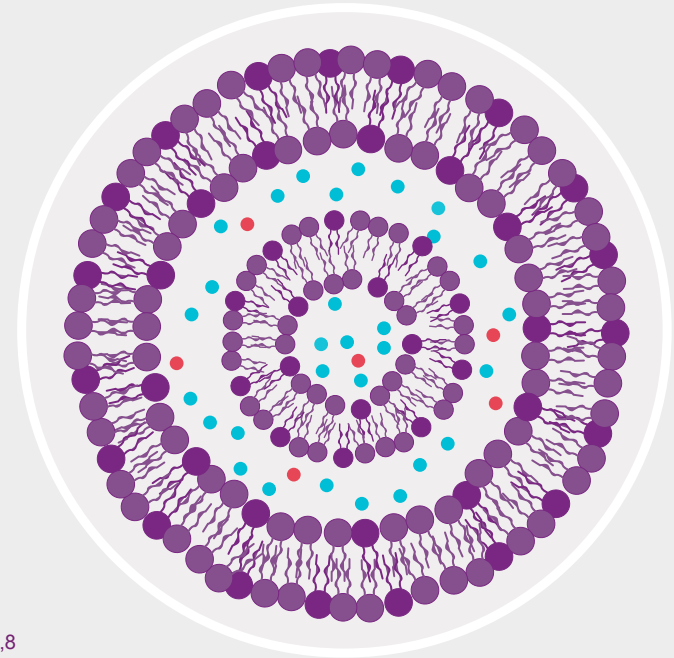
D C

- The advanced technology of Vyxeos Liposomal optimises the delivery of daunorubicin and cytarabine in a synergistic 1:5 molar ratio to **increase anti-tumour activity**[2]

VYXEOS LIPOSOMAL USES ADVANCED DELIVERY TECHNOLOGY TO PROLONG THE SYNERGISTIC DRUG RATIO

SYNERGISTIC RATIO

- Fixed 1:5 molar ratio of daunorubicin and cytarabine within an advanced liposomal formulation[1,3]



- 100 nm bilamellar liposomes[1,8]
- The advanced liposome bilayers comprise a 7:2:1 molar ratio of **DSPC**, **DSPG** and cholesterol[9]
- 1 unit = 0.44 mg daunorubicin plus 1.0 mg cytarabine[3]

DSPC – distearoylphosphatidylcholine
DSPG – distearoylphosphatidylglycerol

VYXEOS LIPOSOMAL SIGNIFICANTLY IMPROVES EFFICACY VS CONVENTIONAL CHEMOTHERAPY* BY OPTIMISING DRUG DELIVERY

High melting point[7] → >99% of the drug remains encapsulated in the liposomes[3]

100 nm bilamellar liposome[1] → Optimal size to penetrate the bone marrow[8]

Negatively charged liposomes[8] → Leukemia cells preferentially bind to negatively charged liposomes[8,9]

PROLONGED SYNERGY

Synergistic molar ratio maintained for a prolonged period of time; over 24 hours after administration[1,3]

HIGH CONCENTRATION

Vyxeos Liposomal accumulates and persists in the bone marrow in high concentrations as shown in animal models[3]

PREFERENTIAL UPTAKE

The liposomes are preferentially taken up by leukaemia cells vs normal bone marrow cells as shown in vitro[3]

After internalisation, Vyxeos liposomes degrade releasing a synergistic ratio of daunorubicin and cytarabine within the intracellular environment[3]

* Comparator arm conventional chemotherapy is 7 + 3 in induction, 5 + 2 in second induction and consolidation where given

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VYXEOS LIPOSOMAL PHARMACOLOGIC ADVANTAGES AND OBSERVED EFFICACY BENEFITS IN HIGH-RISK AML#

High-risk AML defined as newly diagnosed t-AML or AML-MRC

Vyxeos Liposomal has demonstrated vs conventional chemotherapy:*[2]

	VYXEOS LIPOSOMAL	CONVENTIONAL CHEMOTHERAPY*
SIGNIFICANT IMPROVEMENT IN MEDIAN OVERALL SURVIVAL	9.6 months	5.9 months
	One-sided P = .003	
OVERALL SURVIVAL AT (Estimated from Kaplan-Meier curve)	**1 YEAR**	
	41.5%	27.6%
	2 YEARS	
	31.1%	12.3%
	5 YEARS[10]	
	18%	8%
SIGNIFICANTLY HIGHER COMPLETE RESPONSE RATE (CR)	37.3%	25.6%
	Two-sided P = .040	
SIGNIFICANTLY HIGHER OVERALL REMISSION (CR + CRi)	47.7%	33.3%
	Two-sided P = .016	
LOWER EARLY MORTALITY	**30-DAY**	
	5.9%	10.6%
	Two-sided P = .149	
	60-DAY	
	13.7%	21.2%
	Two-sided P = .097	
MORE PATIENTS PROCEED TO TRANSPLANT[10]	35%	25%
	Two-sided P = .098	
OUTCOMES POST TRANSPLANT[10]	Post-transplant survival† outcomes for Vyxeos Liposomal were **52%** at 5 years and **23%** for conventional chemotherapy* at 3 years‡	

* Comparator arm conventional chemotherapy is 7 + 3 in induction, 5 + 2 in second induction and consolidation where given
† Estimated from Kaplan-Meier curve ‡ 5-year figure for conventional chemotherapy was not estimable from the Kaplan-Meier curve. The 3-year figure for Vyxeos Liposomal was 56%

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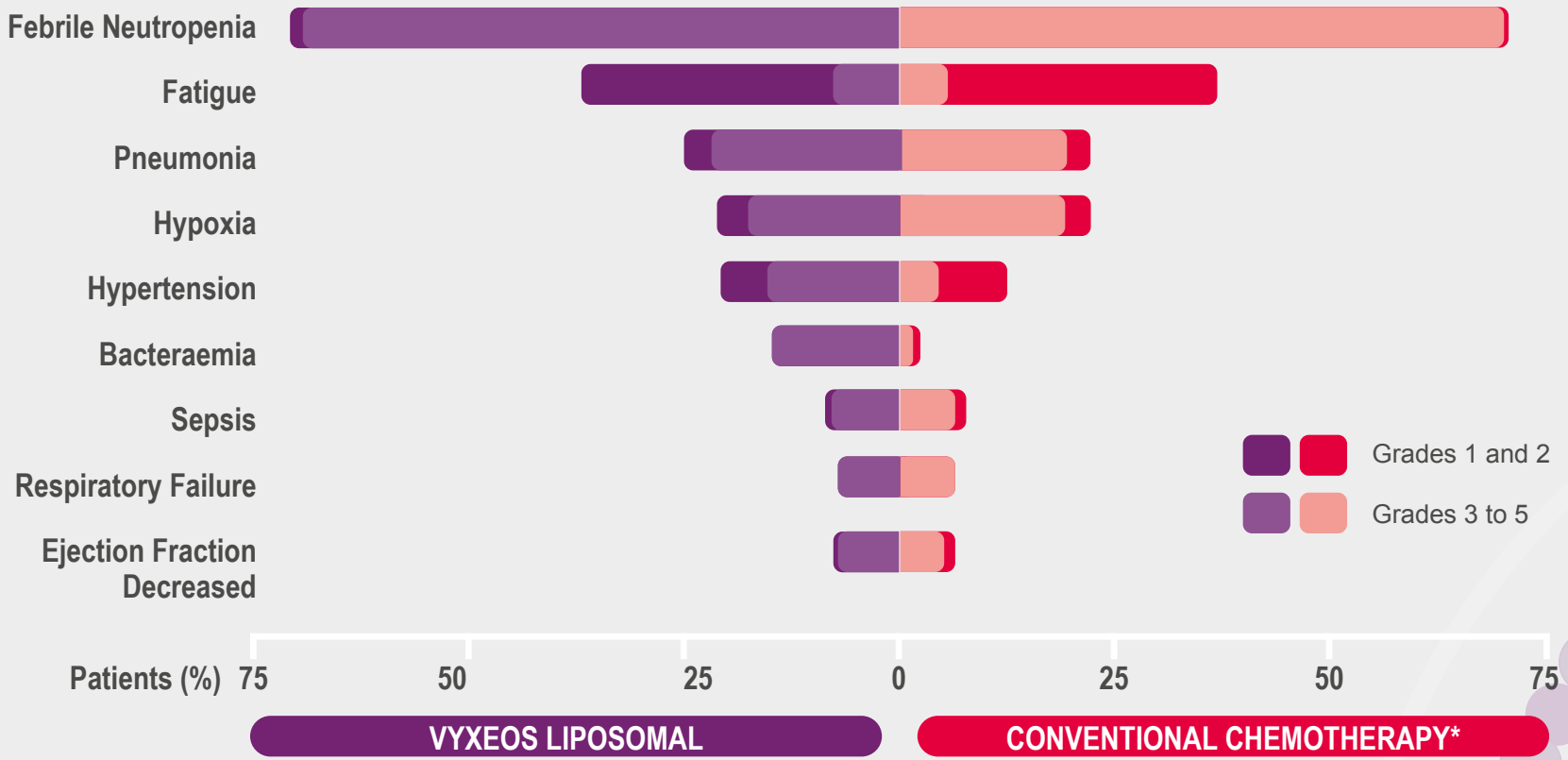
VYXEOS LIPOSOMAL SAFETY PROFILE IS COMPARABLE TO CONVENTIONAL CHEMOTHERAPY*

- Grade 3-5 adverse events (AE) were comparable to conventional chemotherapy* and were similar in frequency and severity[2]
- **Vyxeos Liposomal is associated with prolonged neutropenia and thrombocytopenia so patients may require additional monitoring[3]**

Grade 3-5 Adverse Events (Event Frequency ≥5% in All Patients)[2]



For more information please refer to SmPC/Safety profile

* Comparator arm conventional chemotherapy is 7 + 3 in induction, 5 + 2 in second induction and consolidation where given

VYXEOS LIPOSOMAL CAN BE USED IN BOTH INDUCTION AND CONSOLIDATION[3]

- A full course of Vyxeos Liposomal consists of up to 2 cycles of induction and up to 2 cycles of consolidation[3]

INDUCTION CYCLES

CONSOLIDATION CYCLES

- Post-hoc analysis suggests that Vyxeos Liposomal provides the greatest benefit when used in both induction, and consolidation, where appropriate[2,11]
  - Patients receiving Vyxeos Liposomal for induction and consolidation therapy achieved **25.4 months** median overall survival vs **8.5 months** for conventional chemotherapy* (HR:0.44, 95%CI; 0.25-0.77)[11]

*Comparator arm conventional chemotherapy is 7 + 3 in induction, 5 + 2 in second induction and consolidation where given

VYXEOS LIPOSOMAL DOSING INFORMATION[3]

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Surface area (m^2)	Induction (44/100 mg)/m^2		Consolidation (29/65 mg)/m^2	
	Number of vials (powder)	Volume to withdraw (mL)*	Number of vials (powder)	Volume to withdraw (mL)*
1	1	20	1	13.2
1.02	2	20.4	1	13.4
1.04	2	20.8	1	13.7
1.06	2	21.2	1	14.0
1.08	2	21.6	1	14.2
1.1	2	22	1	14.5
1.12	2	22.4	1	14.8
1.14	2	22.8	1	15.0
1.16	2	23.2	1	15.3
1.18	2	23.6	1	15.6
1.2	2	24	1	15.8
1.22	2	24.4	1	16.1
1.24	2	24.8	1	16.3
1.26	2	25.2	1	16.6
1.28	2	25.6	1	16.9
1.3	2	26	1	17.1
1.32	2	26.4	1	17.4
1.34	2	26.8	1	17.7
1.36	2	27.2	1	17.9
1.38	2	27.6	1	18.2
1.4	2	28	1	18.5
1.42	2	28.4	1	18.7
1.44	2	28.8	1	19.0
1.46	2	29.2	1	19.2
1.48	2	29.6	1	19.5
1.5	2	30	1	19.8
1.52	2	30.4	1	20.0
1.54	2	30.8	2	20.3
1.56	2	31.2	2	20.6
1.58	2	31.6	2	20.8
1.6	2	32	2	21.1
1.62	2	32.4	2	21.4
1.64	2	32.8	2	21.6
1.66	2	33.2	2	21.9
1.68	2	33.6	2	22.1
1.7	2	34	2	22.4
1.72	2	34.4	2	22.7
1.74	2	34.8	2	22.9
1.76	2	35.2	2	23.2
1.78	2	35.6	2	23.5

Surface area (m^2)	Induction (44/100 mg)/m^2		Consolidation (29/65 mg)/m^2	
	Number of vials (powder)	Volume to withdraw (mL)*	Number of vials (powder)	Volume to withdraw (mL)*
1.8	2	36	2	23.7
1.82	2	36.4	2	24.0
1.84	2	36.8	2	24.3
1.86	2	37.2	2	24.5
1.88	2	37.6	2	24.8
1.9	2	38	2	25.0
1.92	2	38.4	2	25.3
1.94	2	38.8	2	25.6
1.96	2	39.2	2	25.8
1.98	2	39.6	2	26.1
2	2	40	2	26.4
2.02	3	40.4	2	26.6
2.04	3	40.8	2	26.9
2.06	3	41.2	2	27.2
2.08	3	41.6	2	27.4
2.1	3	42	2	27.7
2.12	3	42.4	2	27.9
2.14	3	42.8	2	28.2
2.16	3	43.2	2	28.5
2.18	3	43.6	2	28.7
2.2	3	44	2	29.0
2.22	3	44.4	2	29.3
2.24	3	44.8	2	29.5
2.25	3	45	2	29.7
2.26	3	45.2	2	29.8
2.27	3	45.4	2	29.9
2.28	3	45.6	2	30.1
2.29	3	45.8	2	30.2
2.3	3	46	2	30.3
2.32	3	46.4	2	30.6
2.34	3	46.8	2	30.8
2.36	3	47.2	2	31.1
2.38	3	47.6	2	31.4
2.4	3	48	2	31.6
2.42	3	48.4	2	31.9
2.44	3	48.8	2	32.2
2.46	3	49.2	2	32.4
2.48	3	49.6	2	32.7
2.5	3	50	2	33.0

*Rounded up to the nearest 0.1mL

BSA – Body Surface Area

Dose of daunorubicin (mg/m^2) x patient's BSA (m^2)

2.2 mg/mL

=

volume required (mL)

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

RENAL IMPAIRMENT[3]

- No dose adjustment required in mild, moderate or severe renal impairment. There is no experience in end-stage renal disease managed with dialysis.

HEPATIC IMPAIRMENT[3]

- No dose adjustment required for patients with bilirubin level ≤ 50 µmol/L
- There is no experience with Vyxeos Liposomal in patients with hepatic impairment resulting in a bilirubin level greater than 50 µmol/L therefore, no dose recommendations can be made

CARDIOTOXICITY[3]

Cumulative exposure of daunorubicin per course of Vyxeos Liposomal

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

PLEASE NOTE: 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. The relationship between cumulative Vyxeos Liposomal dose and the risk of cardiac toxicity has not been determined[3]

VYXEOS LIPOSOMAL OFFERS A REDUCED INFUSION TIME VS CONVENTIONAL CHEMOTHERAPY[3]

VYXEOS LIPOSOMAL

1 2 3 4 5 6 7

FIRST INDUCTION

Days 1,3,5
44 mg/100 mg per m^2

- 90-min infusion
- 90-min infusion
- 90-min infusion

SECOND INDUCTION AND CONSOLIDATION*

Days 1 and 3
second induction: 44mg/100 mg per m^2
consolidation: 29 mg/65 mg per m^2

- 90-min infusion
- 90-min infusion

CONVENTIONAL CHEMOTHERAPY[2]

1 2 3 4 5 6 7

INDUCTION

Days 1-7
cytarabine 100 mg/m^2/day
continuous infusion

Days 1-3
daunorubicin 60 mg/m^2/day

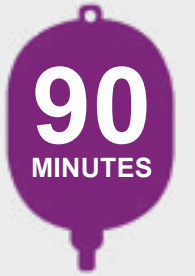
- 15-min IV bolus
- 15-min IV bolus
- 15-min IV bolus

SECOND INDUCTION AND CONSOLIDATION*

Days 1-5
cytarabine 100 mg/m^2/day
continuous infusion

Days 1 and 2
daunorubicin 60 mg/m^2/day

- 15-min IV bolus
- 15-min IV bolus



VYXEOS LIPOSOMAL HAS A 90-MINUTE INFUSION TIME[3]

*where given

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PREPARATION AND ADMINISTRATION[3]

For administration an in-line membrane filter may be used if the minimum pore diameter is at least 15 microns

- Calculate Vyxeos Liposomal dose based on patient's **BSA** and determine the number of vials required

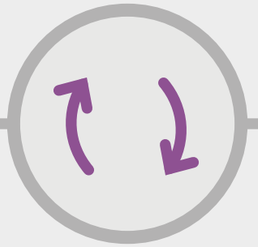
- Remove the vials of Vyxeos Liposomal from the refrigerator
- Equilibrate at room temperature (15-30ºC) for 30 minutes

Do not heat

- Reconstitute each vial with **19 mL of sterile water** for injection using a 20 mL syringe
- 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
- After reconstitution, let rest for 15 minutes

Do not vortex or shake vigorously

- The reconstituted product will be a translucent, purple, homogeneous dispersion, essentially free from visible particulates
- If the reconstituted product is not diluted into an infusion bag immediately, store in refrigerator at **2°C to 8°C for up to 4 hours** prior to infusion time



- Gently invert each vial 5 times prior to withdrawing the reconstituted product for further dilution

Do not vortex or shake vigorously

- Aseptically withdraw the calculated volume of reconstituted Vyxeos Liposomal from the vial(s) with a sterile syringe and transfer it to an infusion bag containing 500 mL of 0.9% sodium chloride injection or 5% glucose injection. There may be residual product remaining in the vial. **Discard unused portion**
- **Gently invert** the bag to mix the solution after refrigeration
- If the diluted infusion solution is not used immediately, store in refrigerator at **2°C to 8°C for up to 4 hours**

For a step-by-step demonstration of how to prepare and administer Vyxeos Liposomal visit www.vyxeos.eu

BSA – Body Surface Area

Up to 4 hour stability when stored at 2°C to 8°C
(storage time does not include time for reconstitution or infusion)

PRESCRIBING INFORMATION

Vyxeos® Liposomal 44mg/100mg powder for concentrate for solution for infusion (daunorubicin and cytarabine)

Please refer to local Summary of Product Characteristics (SmPC) before prescribing

Presentation: Purple lyophilised cake of powder for concentrate for solution for infusion. Each vial contains 44 mg daunorubicin and 100 mg 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.

Indication: For the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

Dosage and administration: Treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Do not interchange Vyxeos liposomal with other daunorubicin and/or cytarabine containing products. For intravenous infusion use only. An in-line membrane filter may be used provided the minimum pore diameter is greater than or equal to 15 µm. Do not administer via an intramuscular, intrathecal, or subcutaneous route. *Refer to full SmPC for detailed information on preparation of solution for infusion. Recommended dosing schedule for induction of remission*: 44 mg/100 mg/m^2, administered intravenously over 90 minutes on days 1, 3, and 5 as the first course of induction therapy; then on days 1 and 3 as subsequent course of induction therapy, if needed. *Recommended dosing schedule for consolidation:* Administer first consolidation cycle 5 to 8 weeks after the start of the last induction. Recommended dosing schedule 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. Dose adjustments during treatment may be required in hypersensitivity symptoms and cardiotoxicity. Assessment of cardiac function prior to start of treatment is recommended. Patients should be monitored for haematologic response and toxicities. *Renal impairment***:** No dose adjustment required in mild, moderate or severe renal impairment. There is no experience in end-stage renal disease managed with dialysis. *Hepatic impairment:* No dose adjustment required for bilirubin level less than or equal to 50 µmol/L. There is no experience in hepatic impairment resulting in a bilirubin level greater than 50 µmol/L. *Elderly population (≥65 years):* No dose adjustment required.

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions: Do not substitute or interchange with other daunorubicin and/or cytarabine-containing products. Severe myelosuppression and serious or fatal haemorrhagic events have been reported. Time to recovery of ANC and platelets may be prolonged and require additional monitoring. Monitor blood counts regularly until recovery. Prophylactic anti-infectives may be administered during the period of profound neutropenia until ANC returns to 500/µL or greater. Cardiotoxicity is a known risk; prior therapy with anthracyclines, pre-existing cardiac disease, previous radiotherapy of the mediastinum, or concomitant use of cardiotoxic products may increase the risk. Hepatic impairment may increase the risk of toxicity. Evaluation of hepatic function is recommended prior to administration and periodically during treatment. Monitor blood uric acid levels and initiate appropriate therapy if hyperuricemia develops. Each vial of Vyxeos liposomal contains 100 mg of copper gluconate. Only use in patients with a history of Wilson's disease or other copper-related disorder if the benefits outweigh the risks. Serious hypersensitivity reactions including anaphylactic reactions have been reported with daunorubicin and cytarabine. Avoid administration of live or live-attenuated vaccines. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. Gastrointestinal mucositis and/or diarrhoea frequently occur and may influence the absorption of oral accompanying medicinal products.

Interactions: Do not administer in combination with cardiotoxic agents unless cardiac function is closely monitored. Monitor hepatic function more frequently if co-administered with hepatotoxic agents.

Pregnancy, lactation and fertility: There are no data on use in pregnant women. Do not use during pregnancy unless the benefit of treatment outweighs the risk. It is not known if Vyxeos liposomal is excreted in human milk therefore advise mothers to discontinue breastfeeding during therapy. Advise patients to avoid becoming pregnant while receiving Vyxeos liposomal. Male patients and women of childbearing potential must use an effective method of contraception during treatment and for 6 months following the last dose. Male fertility may be compromised by treatment.

Undesirable effects: ***Please refer to the full SmPC for the complete list.*** Hypersensitivity, febrile neutropenia, oedema, diarrhoea/colitis, mucositis, fatigue, musculoskeletal pain, abdominal pain, decreased appetite, cough, headache, chills, arrhythmia, pyrexia, sleep disorders, and hypotension are the most frequently occurring adverse reactions (ADRs). Infection, cardiotoxicity and haemorrhage are the most serious and frequently occurring ADRs.

Storage and Handling: Store in a refrigerator (2°C - 8°C). Vyxeos liposomal is cytotoxic; unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

Legal category: Prescription only medicine (POM). **Marketing authorisation number**: EU/1/18/1308/001 **Package quantity and Cost**: carton containing 1 × 50 mL vial. Refer to local prescribing information for price. **Further information** is available from **Marketing Authorisation Holder**: Jazz Pharmaceuticals Ireland Ltd., 5th Floor, Waterloo Exchange, Waterloo Road, Dublin D04 E5W7, Ireland.

Date of revision: July 2022 INT-VYX-1900009

Vyxeos® is a registered trademark of Celator Pharmaceuticals, Inc. (a Jazz Pharmaceuticals subsidiary)

For country specific information please refer to your local SmPC or Product Monograph

Adverse events should be reported.
Healthcare professionals are asked to report any adverse events via their national reporting system (see Section 4.8 of SmPC).
Adverse events should also be reported to Jazz Pharmaceuticals by email to medinfo-int@jazzpharma.com or phone via +3531 968 1631 (may include an international call charge).

PI

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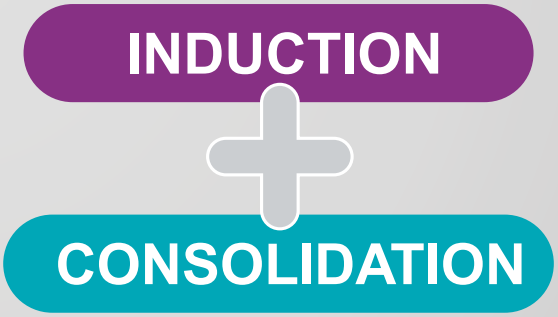
Vyxeos Liposomal is the first dual-drug advanced liposomal formulation of daunorubicin and cytarabine[1]

Superior overall median survival vs conventional chemotherapy* in patients with high-risk AML[#2]

Increased overall survival without increasing toxicity burden vs conventional chemotherapy*[2]



* Comparator arm conventional chemotherapy is 7 + 3 in induction, 5 + 2 in second induction and consolidation where given

High-risk defined as newly diagnosed t-AML or AML-MRC

Jazz Pharmaceuticals

INT-VYX-2200129
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