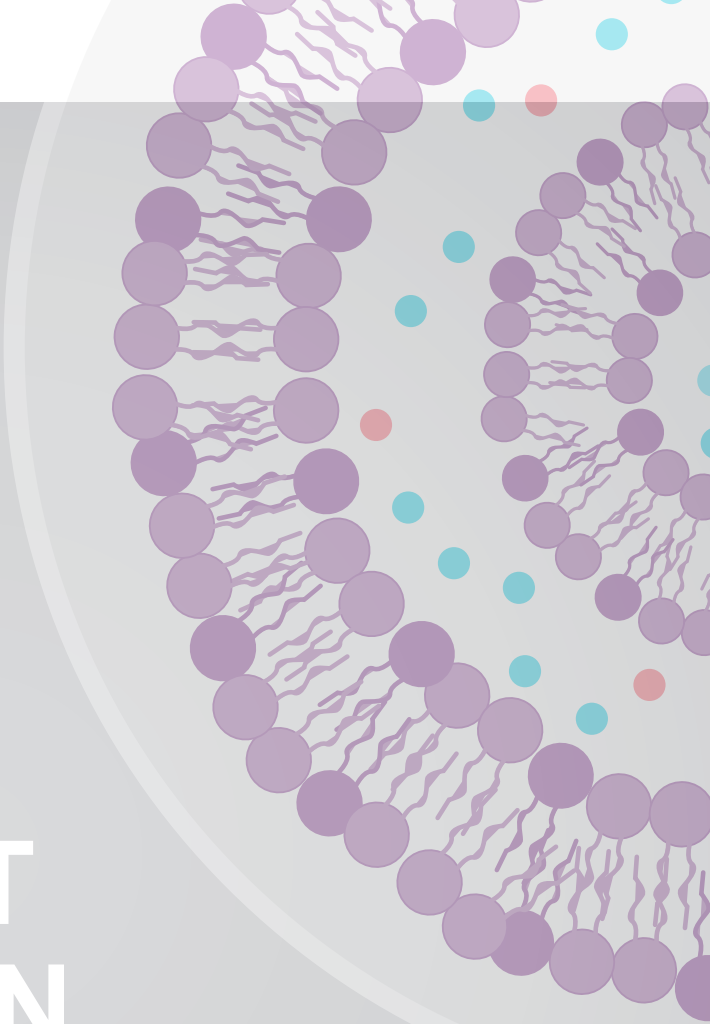


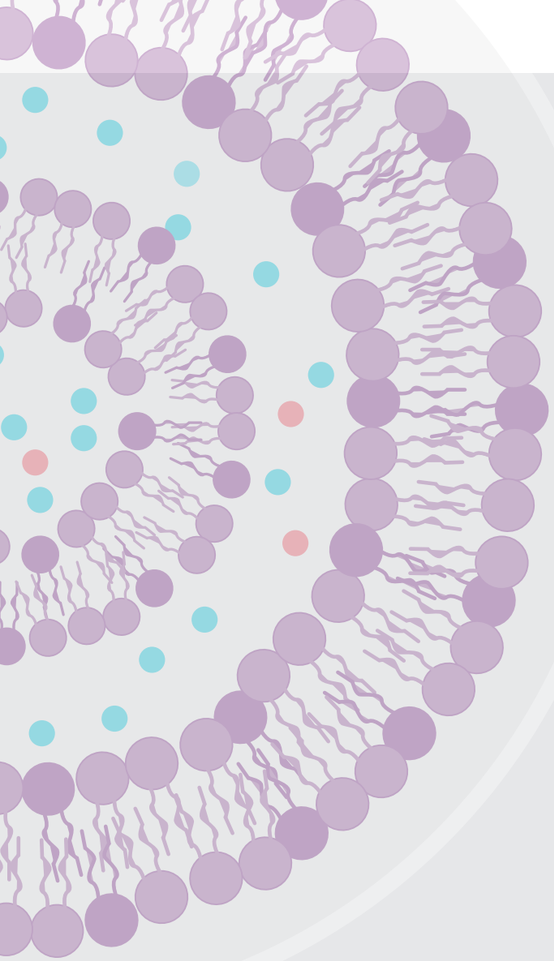
PHARMACIST INFORMATION

Vyxeos® Liposomal

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

daunorubicin / cytarabine

Prescribing information and adverse event reporting details can be found on page 14 of this booklet



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]

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)[7]

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

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[3-6]

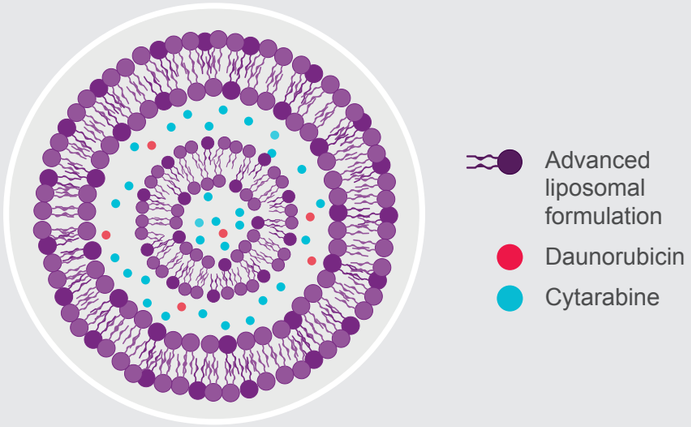
D C

- 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[1,7]



- 100 nm bilamellar liposomes[1]
- 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[7]

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[7]

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[8,10]

PROLONGED SYNERGY

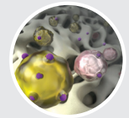
Synergistic molar ratio maintained for a prolonged period of time; over 24 hours after administration†[4]

HIGH CONCENTRATION

Vyxeos Liposomal accumulates and persists in the bone marrow in high concentrations†[8]

PREFERENTIAL UPTAKE

The liposomes are preferentially taken up by leukaemia cells vs normal bone marrow cells†[7]



† Shown in animal models

After internalisation, Vyxeos liposomes degrade releasing a synergistic ratio of daunorubicin and cytarabine within the intracellular environment[7]

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

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

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

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

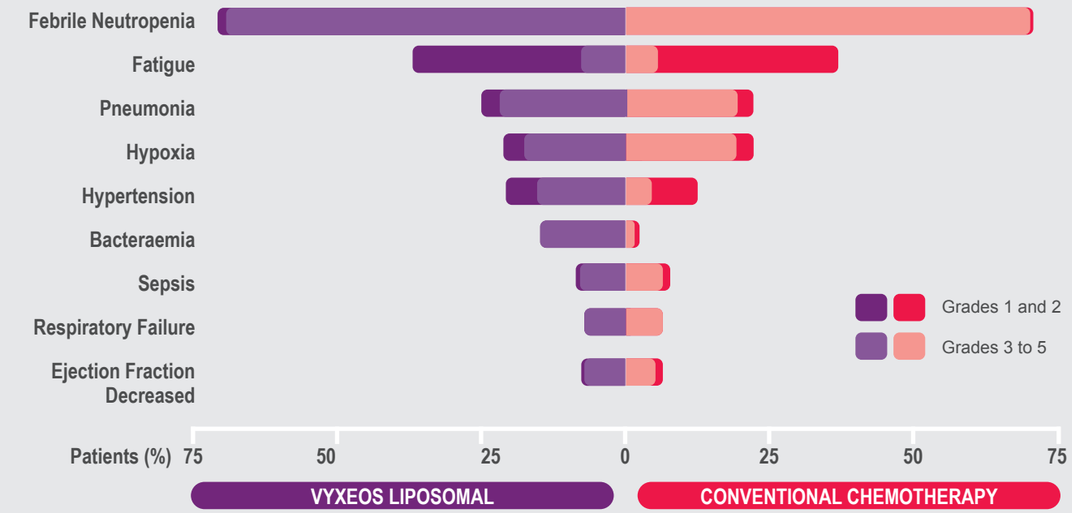
	VYXEOS LIPOSOMAL	CONVENTIONAL CHEMOTHERAPY*
SIGNIFICANT IMPROVEMENT IN MEDIAN OVERALL SURVIVAL	9.6 months	5.9 months
	One-sided P = .003	
	31% reduction in relative risk of death for patients treated with Vyxeos Liposomal vs conventional chemotherapy	
IMPROVED OVERALL SURVIVAL AT	**12 MONTHS**	
	41.5%	27.6%
	One-sided P = .009	
	24 MONTHS	
	31.1%	12.3%
	One-sided P = .009	
SIGNIFICANTLY HIGHER COMPLETE RESPONSE RATE	37.3%	25.6%
	Two-sided P = .0.40	
SIGNIFICANTLY HIGHER OVERALL REMISSION	47.7%	33.3%
	Two-sided P = .016	
LOWER 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	34%	25%
	Two-sided P = .098	
IMPROVED OUTCOMES POST TRANSPLANT	Post-hoc analysis suggests that Vyxeos Liposomal may improve transplant outcomes vs conventional chemotherapy*, hazard ratio = 0.46 (95% CI 0.24-0.89); 1-sided P = .009	

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

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[7]**

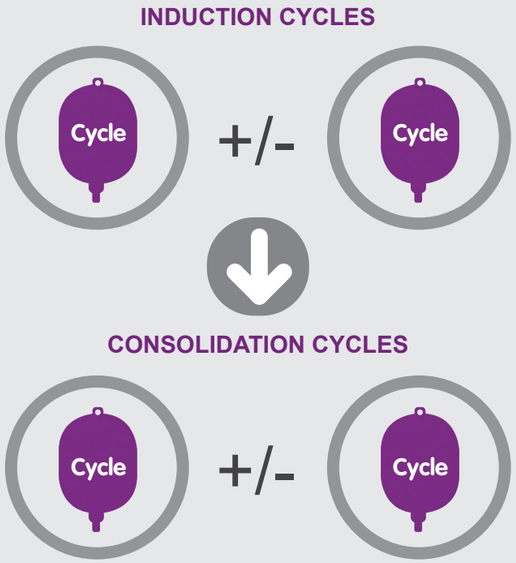
Grade 3-5 Adverse Events (Event Frequency ≥5% in All Patients)[2]



For more information please refer to SmPC/Safety profile

VYXEOS LIPOSOMAL CAN BE USED IN BOTH INDUCTION AND CONSOLIDATION[11]

- A full course of Vyxeos Liposomal consists of up to 2 cycles of induction and up to 2 cycles of consolidation[7]



- 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[11]

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

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

2.2 mg/mL

=

volume required (mL)

BSA – Body Surface Area

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

RENAL IMPAIRMENT[7]

- No dose adjustment required for mild or moderate renal impairment
- There is no experience with Vyxeos Liposomal in patients with severe renal impairment or end stage renal disease, therefore, no dose recommendations can be made

HEPATIC IMPAIRMENT[7]

- 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[7]

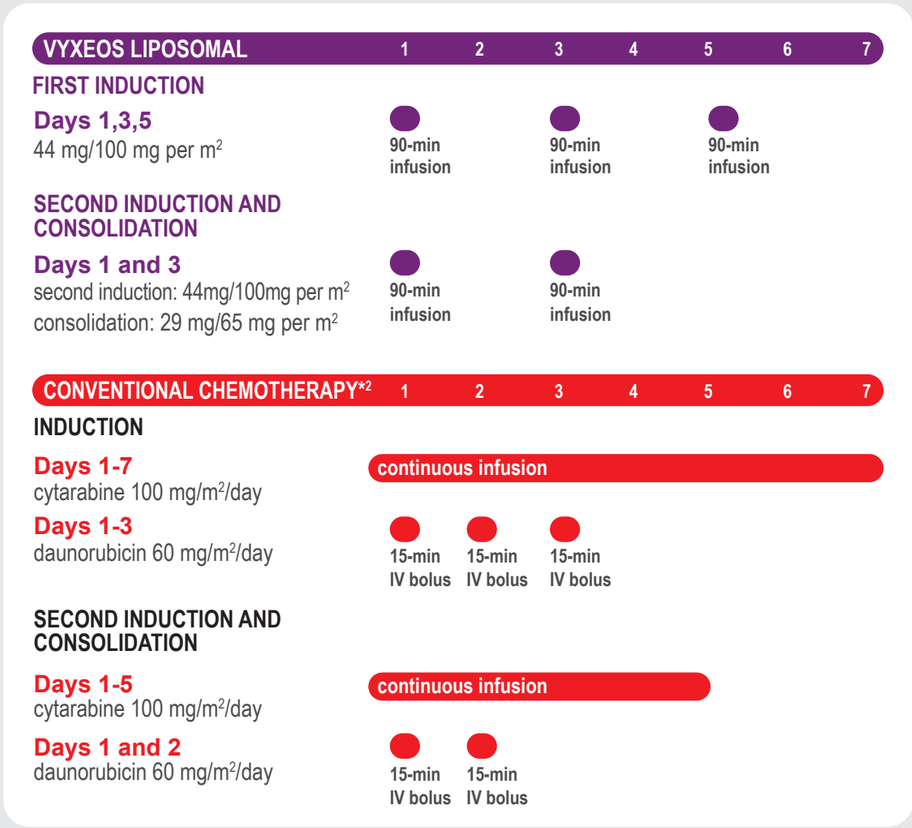
Cumulative exposure of daunorubicin per course of Vyxeos Liposomal

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(s)	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 [7]

For more information please refer to SmPC/Safety profile

VYXEOS LIPOSOMAL OFFERS A REDUCED INFUSION TIME VS CONVENTIONAL CHEMOTHERAPY*[7]



VYXEOS LIPOSOMAL HAS A 90-MINUTE INFUSION TIME[7]

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

PREPARATION AND ADMINISTRATION[7]

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

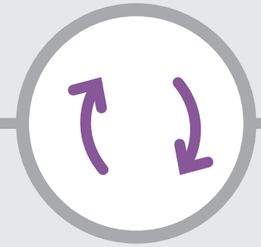
- Remove the vials of Vyxeos Liposomal from the refrigerator
- Equilibrate at room temperature (15-30ºC) for 30 minutes

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
- 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

Do not vortex or shake vigorously



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

- 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

PRESCRIBING INFORMATION

Vyxeos® Liposomal 44mg/100mg powder for concentrate for solution for infusion
(Daunorubicin and cytarabine)
Please refer to the Summary of Product Characteristics before prescribing.

Presentation: Purple lyophilised cake of powder for concentrate for solution for infusion.
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. **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**: For intravenous infusion use only. An in-line membrane filter may be used provided the minimum pore diameter of the filter is greater than or equal to 15 µm. It must not be administered via an intramuscular, intrathecal, or subcutaneous route. *Refer to the full SmPC for detailed information on preparation of solution for infusion*. Treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products. *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:* The first consolidation cycle should be administered 5 to 8 weeks after the start of the last induction. The 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. *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 in patients with severe renal impairment (CrCL 15 mL/min to 29 mL/min) or end-stage renal disease. It should only be used in patients with severe renal impairment if the benefits outweigh the risks. *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 in patients with hepatic impairment resulting in a bilirubin level greater than 50 µmol/L. It should only be used in patients with severe hepatic impairment if the benefits outweigh the risks. *Elderly population (≥65 years):* No dose adjustment is required. *Paediatric population*: The safety and efficacy in children aged 0–18 years has not yet been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings, precautions and interactions**: Do not substitute or interchange with other daunorubicin and/or cytarabine-containing products. Severe myelosuppression and serious or fatal haemorrhagic events have been reported. Due to the long plasma half-life of Vyxeos liposomal, time to recovery of ANC and platelets may be prolonged and require additional monitoring. Prophylactic anti-infectives 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. Blood counts should be regularly monitored until recovery. As 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. Hepatotoxic medicinal products may impair liver function and increase toxicity. Evaluation of hepatic and renal function is recommended prior to administration and periodically during treatment. Blood uric acid levels should be monitored and appropriate therapy initiated if hyperuricemia develops. Each vial of Vyxeos liposomal contains 100 mg of copper gluconate. It should only be used in patients with a history of Wilson's disease or other copper-related disorder if the benefits outweigh the risks. To avoid local tissue necrosis care should be taken to ensure that there is no extravasation of Vyxeos liposomal during administration. Administration of live or live-attenuated vaccines should be avoided. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. The absorption of oral accompanying medicinal products may be considerably influenced by gastrointestinal mucositis and/or diarrhoea frequently occurring in association with intensive chemotherapy. **Pregnancy, lactation and fertility:** There are no data on use in pregnant women. It should not be used during pregnancy unless the benefit of treatment outweighs the risk. It is not known if Vyxeos liposomal is excreted in human milk therefore mothers should be advised to discontinue breastfeeding during therapy. Patients should be advised 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 of undesirable effects.*** The most frequently occurring adverse reactions were hypersensitivity, febrile neutropenia, oedema, diarrhoea/colitis, mucositis, fatigue, musculoskeletal pain, abdominal pain, decreased appetite, cough, headache, chills, arrhythmia, pyrexia, sleep disorders, and hypotension. The most serious and frequently occurring ADRs were infection, cardiotoxicity and haemorrhage. **Overdose**: There is no specific antidote for overdose and treatment should be symptomatic. **Storage and Handling**: Store in a refrigerator (2°C - 8°C). Shelf life of unopened vials: 2 years. Keep vial in the original carton to protect from light and store in an upright position. Vyxeos liposomal is a cytotoxic medicinal product intended for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents. **Legal category**: POM. **Marketing authorisation number**: EU/1/18/1308/001 **Package quantity and Cost**: carton containing 1 × 50 mL vial. Price differs across countries. Further information is available from the **Marketing Authorisation Holder**: Jazz Pharmaceuticals Ireland Ltd., 5th Floor, Waterloo Exchange, Waterloo Road, Dublin D04 E5W7, Ireland. **Date of preparation:** November 2019.
INT-VYX-1900009
Vyxeos® is a registered trade mark.
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 suspected adverse events via their national reporting system.
In the United Kingdom reporting forms and information can be found at:
https://yellowcard.mhra.gov.uk/
Adverse events should also be reported to Jazz Pharmaceuticals by email to
aereporting@jazzpharma.com
or by fax to +44 (0) 1865 598765

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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]

INDUCTION

CONSOLIDATION

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

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

INT-VYX-2000010
Date of Preparation: January 2020

Jazz Pharmaceuticals®