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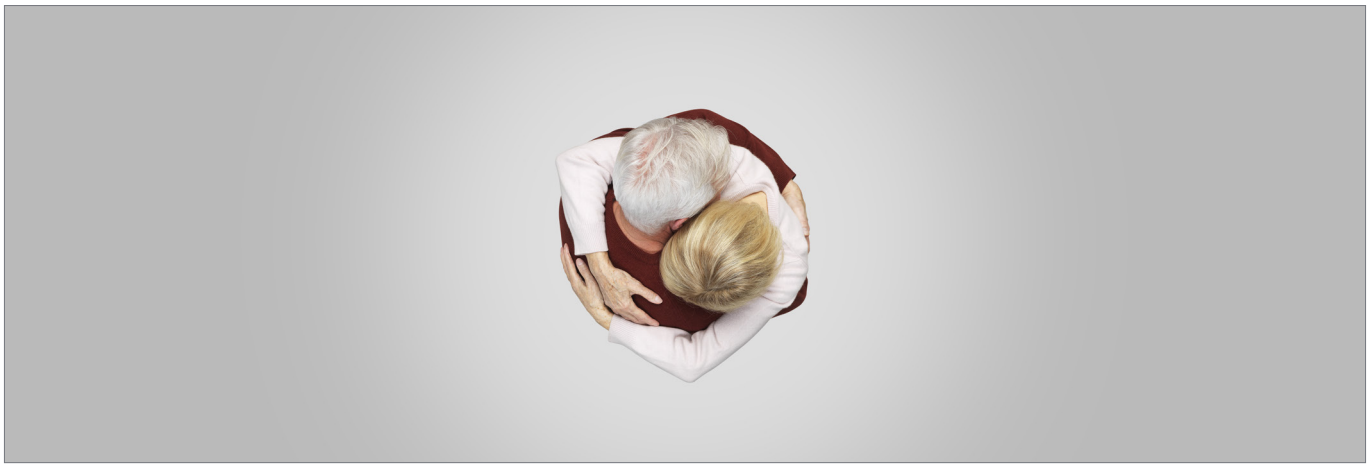
REAL-WORLD TREATMENT OUTCOMES IN ADULTS WITH HIGH-RISK* ACUTE MYELOID LEUKEMIA

Highlights of a Symposium sponsored by Jazz Pharmaceuticals presented during the 4th Annual Meeting of the International Academy of Clinical Hematology (IACH) Virtual Congress, where the faculty reviewed recent Vyxeos liposomal® (daunorubicin 44 mg/cytarabine 100 mg; Jazz Pharmaceuticals) outcomes data and real-world evidence in high-risk* acute myeloid leukemia.



Introduction

Patients with high-risk* acute myeloid leukemia (AML), defined as newly diagnosed, therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC), historically have a poor prognosis and remain therapeutic challenges.[1] Here we present a summary of faculty presentations from a Jazz Pharmaceuticals-sponsored Symposium presented during the 4th Annual Meeting of the International Academy of Clinical Hematology, which review some of the most recent outcomes data and real-world evidence evaluating treatment with Vyxeos liposomal (formerly known as CPX-351),[2] a dual-drug liposomal encapsulation of cytarabine and daunorubicin, in adults with newly diagnosed high-risk* AML.

Vyxeos liposomal treatment contributes to long-term overall survival and higher remission rates than 7+3 therapy in high-risk* acute myeloid leukemia[4]

The pivotal randomized, multicenter phase 3 trial compared Vyxeos liposomal with conventional cytarabine plus daunorubicin chemotherapy (7+3 regimen) in older patients (60–75 years of age) with high-risk* AML.[3] Patients (n=309) were randomly assigned 1:1 to receive Vyxeos liposomal or 7+3 therapy for up to 2 induction cycles and up to 2 consolidation cycles of the same regimen.[3]

After a median follow-up of 20.7 months, Vyxeos liposomal significantly improved overall survival (OS; primary outcome) vs 7+3 therapy (median OS, 9.56 vs 5.95 months, respectively; hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.52–0.90; 2-sided P=0.005).[2,3] The overall remission rate (complete remission [CR] or CR with incomplete neutrophil or platelet recovery [CRi]) was also significantly higher with Vyxeos liposomal vs 7+3 therapy (47.7% vs 33.3%, respectively; 2-sided P=0.016).[3] The incidences of non-hematologic adverse events were comparable in the Vyxeos liposomal and 7+3 treatment groups, despite a longer treatment phase and prolonged time to neutrophil and platelet count recovery (in responders after initial induction) with Vyxeos liposomal (median: 35 and 36.5 days, respectively) vs 7+3 treatment (median: 29 and 29 days, respectively).[3] Prolonged thrombocytopenia and neutropenia is consistent with prolonged myelosuppression and patients may require additional monitoring. The most frequently reported adverse events (Grade 3–5) in the Vyxeos liposomal and 7+3 treatment groups were febrile neutropenia (68.0% vs 70.9%), pneumonia (19.6% vs 14.6%), and hypoxia (13.1% vs 15.2%; **Figure 1**).[3] Early mortality rates with Vyxeos liposomal and 7+3 treatment were 5.9% and 10.6% (two-sided P=0.149) through Day 30 and 13.7% and 21.2% (two-sided P=0.097) through Day 60.[3]

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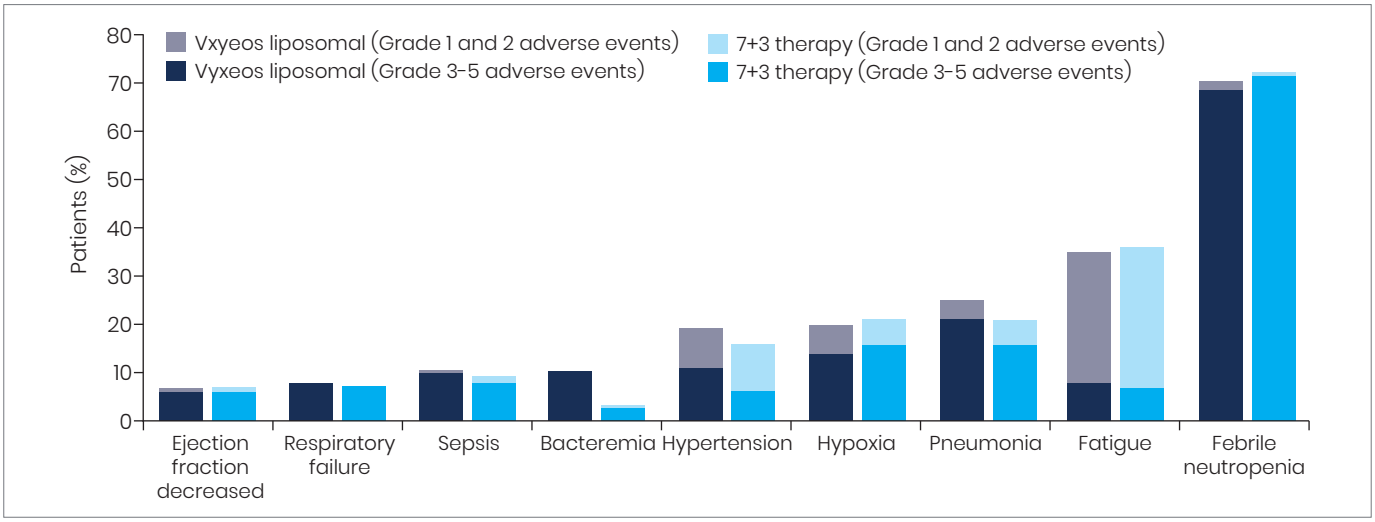
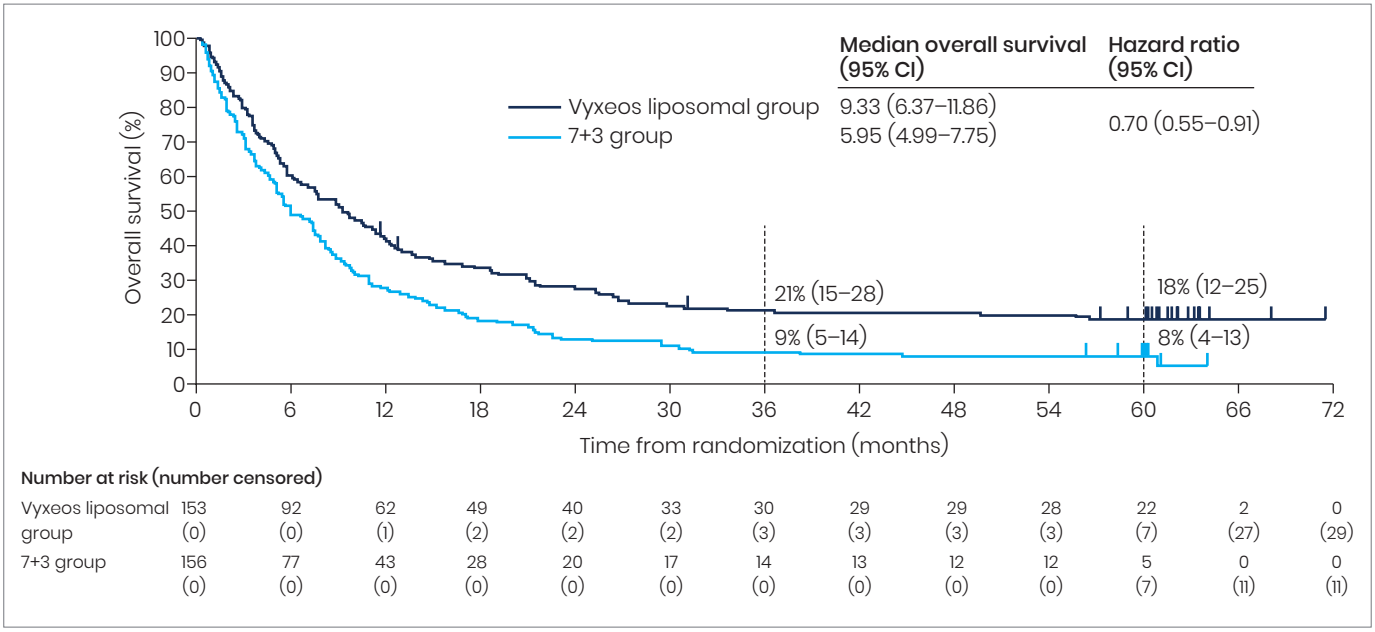
Figure 1. Most frequently reported adverse events in patients with high-risk* AML receiving Vyxeos liposomal or conventional chemotherapy (pivotal phase 3 trial).[3]



AML, acute myeloid leukemia.
The percentage of patients with Grade 1–2 and Grade 3–5 events are shown for all events that occurred in >5% of patients in either treatment group as Grade 3–5 events.

Figure 2. Kaplan-Meier-estimated overall survival rates at 3 and 5 years in patients with high-risk* AML.[4]



Number at risk (number censored)

Vyxeos liposomal group	153 (0)	92 (0)	62 (1)	49 (2)	40 (2)	33 (2)	30 (3)	29 (3)	29 (3)	28 (3)	22 (7)	2 (27)	0 (29)
7+3 group	156 (0)	77 (0)	43 (0)	28 (0)	20 (0)	17 (0)	14 (0)	13 (0)	12 (0)	12 (0)	5 (7)	0 (11)	0 (11)

AML, acute myeloid leukemia; CI, confidence.
Reprinted from Lancet JE, et al. CPX-351 versus cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial. Lancet Haematol. 2021;8(7):e481-e491, with permission from Elsevier.

In a prespecified final analysis of OS in the intent-to-treat population, improvements in OS with Vyxeos liposomal vs conventional 7+3 chemotherapy were maintained over 5 years of follow-up.[4] Post hoc exploratory analyses also showed maintenance of improved OS vs 7+3 therapy across age subgroups, among patients who achieved CR or CRi, and in those who underwent allogeneic hematopoietic stem cell transplantation (HSCT).[4] Overall, after a median follow-up of 60.91 months in the Vyxeos liposomal group and 59.93 months in the 7+3 treatment group, the median OS was 9.33 months (95% CI: 6.37–11.86; including an extra pre-median death discovered after data cutoff) with Vyxeos liposomal and 5.95 months (95% CI: 4.99–7.75) with 7+3 therapy (HR: 0.70; 95% CI: 0.55–0.91; **Figure 2**).[4] Five-year OS estimates were 18% (95% CI: 12–25%) in the Vyxeos liposomal group and 8% (95% CI: 4–13%) in the 7+3 therapy group.[4]

In a post hoc analysis of OS at 3 years, OS landmarked from the date of HSCT was 56% (95% CI: 42–68) with Vyxeos liposomal treatment and 23% with 7+3 therapy (95% CI: 11–37).[4] Five-year estimates were not available as the follow-up time from date of HSCT was less than 5 years.[4] In a post hoc exploratory analysis, in patients who received Vyxeos liposomal and proceeded to HSCT, OS was maintained above 50% at 5 years post-randomization.[4] Overall, the authors concluded that the results highlight potential long-term survival benefits of treatment with Vyxeos liposomal in this older adult population.[4]

The French real-life experience using Vyxeos liposomal to treat high-risk* acute myeloid leukemia

A recent, retrospective study evaluated the efficacy and safety of Vyxeos liposomal treatment in 103 adult patients (median age: 67 years; range, 20–83) from 12 centers in France with newly diagnosed, untreated high-risk* AML.[5] At baseline, 26.2% had t-AML and 71.8% had AML-MRC.[5]

The overall response rate (ORR: CR+CRi) after induction was 59.2% (61/103), and the median OS was 16.1 months (range, 13.1–16.7) after a median follow-up of 8.6 months.[5] Among patients who achieved CR or CRi, minimal residual disease (MRD) was evaluable in 28 patients at the time of first consolidation cycle. Of these, 57.1% (16/28) reached a complete molecular response defined as an MRD $<10^{-3}$.[5]

Patients who underwent allogeneic HSCT had a significantly longer median OS than non-transplanted patients (transplanted patients, median OS not reached vs non-transplanted patients, median OS 9.3 months [range, 4.4–14.2 months]; P<0.001).[5]

The study confirmed the efficacy and acceptable safety profile of Vyxeos liposomal treatment observed in the phase 3 trial.[3,5] However, several adverse events not reported in the pivotal clinical trial were identified, including gastrointestinal toxicities (50.5%), cutaneous rash (25.2%) and alopecia (10.7%).[5] Median times to neutrophil recovery (>0.5 x 10^9/L) and platelet recovery (>20 x 10^9/L) after first induction were 29 days and 28 days, respectively. Early mortality rates at Days 30 and 60 were 6% and 8%, respectively.[5] Among the 36 patients that underwent HSCT, mortality rate at Day 100 was 3%.[5]

Real-life evidence of Vyxeos liposomal outcomes from an Italian compassionate use program

Physicians in Italy evaluated the clinical activity of Vyxeos liposomal in 71 patients (median age: 66 years; range, 52–79) with high-risk* AML who were enrolled in an Italian compassionate use program across 31 centers.[6] At baseline, 18.8% of patients had previous myelodysplastic syndrome (MDS)-related changes, 31% had t-AML and 50.2% had secondary AML.[6] Treatment was performed in accordance with the regimen followed in the pivotal phase 3 trial.[6]

The overall CR+CRi rate at the end of treatment was 70.4% (50/71; **Figure 3**).[8] Median follow-up was 11 months (95% CI: 10.47–11.53) and the 12-month OS was 68.6% (median OS not reached).[6] In a landmarked analysis, twelve-month OS in patients receiving HSCT consolidation after achieving first CR (40%; 20/50) was 100% compared with 70.5% in patients not receiving HSCT after first CR (P=0.011).[6] Allogeneic HSCT performed after achieving first CR was the only independent predictor of longer survival (P<0.05).[6] Of patients who achieved CR/CRi and had MRD testing, 37.5% (15/40) undergoing multiparameter flow cytometric [MFC]-MRD analysis and 55.3% (21/38) evaluated with Wilms' tumor gene [WT1]-based MRD assessment tested negative.[6] Although there was a trend towards reduced relapse risk for patients with MFC-MRD-negative CR, MRD-negativity did not result in better clinical outcome, possibly due to the small sample size.[6]

Most of the adverse events were infections, with a fever of unknown origin reported in 28% of patients, sepsis in 28% and pneumonia in 11.3%.[6] Median time to absolute neutrophil count recovery (>0.5x10^9/L) was 38 days (range, 12–60) and median time to platelet recovery (>25x10^9/L) was 28 days (range, 12–60). The 60-day treatment-related mortality rate was 7% (5/71). [6]

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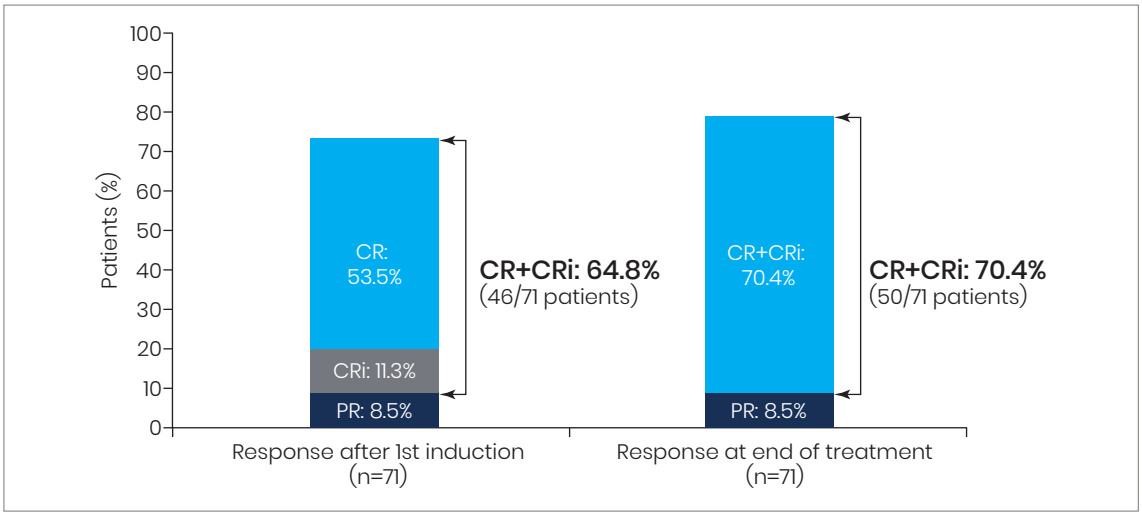
Figure 3. Complete response rates in patients with high-risk* AML patients receiving Vyxeos liposomal in an Italian compassionate use program.[6]



AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete neutrophil or platelet recovery; CUP, compassionate use program; PR, partial response.

Table 1. Age-range of patient populations in the pivotal phase 3 trial and real-world studies of Vyxeos liposomal for the treatment of high-risk AML in France and Italy.[4–6]

	Pivotal phase 3 trial[4] (N=309)	French retrospective study[5] (N=103)	Italian CUP[6] (N=71)
Median age, years (range)	Median: 68 (64–71)	Median: 67 (20–83)	Median: 66 (52–79)

AML, acute myeloid leukemia; CUP, compassionate use program.

Overall, the authors concluded that these results confirm the efficacy observed in the pivotal phase 3 clinical trial, demonstrating that Vyxeos liposomal is an effective induction regimen for patients with high-risk* AML treated with curative aim.[6] The authors also concluded that treatment with Vyxeos liposomal "can induce good quality remissions with acceptable toxicity in most patients",[6] and that the lower incidence of severe complications expected with Vyxeos liposomal compared with conventional treatment may reasonably allow more elderly patients with high-risk* AML to receive intensive induction and subsequent HSCT consolidation.[6]

Conclusion

Pivotal phase 3 data demonstrate that Vyxeos liposomal treatment yielded a superior median OS vs conventional 7+3 therapy in high-risk* AML patients,[3] with long-term data showing that this survival benefit can be maintained at 5 years of follow-up.[5]

Moreover, independent studies confirm the efficacy and safety of Vyxeos liposomal in adult patients with high-risk* AML treated in real-world settings (**Table 1**) and provide additional insight beyond the pivotal clinical trial, including data on CR with MRD-negativity and further safety information.[5,6] In conclusion, Vyxeos liposomal treatment may lay the foundation for increased long-term survival prospects in patients with newly diagnosed high-risk* AML.[4]

If you would like to view the touchSYMPOSIUM HIGHLIGHTS, please visit:
www.touchoncologytmc.com/tsh-treating-high-risk-acute-aml

*High-risk AML is defined as newly diagnosed, therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)

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References

1. Granfeldt Østgård LS, Medeiros BC, Sengeløv H, et al. Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a national population-based cohort study. *J Clin Oncol.* 2015;33(31):3641-3649.
2. Vyxeos liposomal 44 mg/100 mg powder for concentrate for solution for infusion [summary of product characteristics]. Dublin, Ireland: Jazz Pharmaceuticals Ireland Ltd; 2021. Available at https://www.medicines.org.uk/emc/product/9442/smpc (last accessed 05 November 2021).
3. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol.* 2018;36(26):2684-2692.
4. Lancet JE, Uy GL, Newell LF, et al. CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial. *Lancet Haematol.* 2021;8(7):e481-e491.
5. Chiche E, Rahmé R, Bertoli S, et al. Real-life experience with CPX-351 and impact on the outcome of high-risk AML patients: a multicentric French cohort. *Blood Adv.* 2021;5(1):176-184.
6. Guolo F, Fianchi L, Minetto P, et al. CPX-351 treatment in secondary acute myeloblastic leukemia is effective and improves the feasibility of allogeneic stem cell transplantation: results of the Italian compassionate use program. *Blood Cancer J.* 2020;10(10):96.

International Core 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/m2, 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/m2, 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. **Job Code:** INT-VYX-1900009.
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