

Vyxeos[®]

Liposomal Daunorubicin-Cytarabine

Indication

Treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or Secondary AML (prior MDS/MPN/CMML or AML with myelodysplasia related changes (AML-MRC)).

(NICE TA552)

ICD-10 codes

Codes with prefix C92, C92.8

Regimen details

First induction (cycle 1)

Day	Drug	Dose	Route
1, 3 and 5	Daunorubicin and Cytarabine (Vyxeos)	44 mg/m ² 100 mg/m ²	IV infusion

Second induction (cycle 2 if required)

Day	Drug	Dose	Route
1 and 3	Daunorubicin and Cytarabine (Vyxeos)	44 mg/m ² 100 mg/m ²	IV infusion

Consolidation (up to 2 cycles)

Recommended for patients achieving remission who have recovered neutrophils $> 0.5 \times 10^9/L$.

Day	Drug	Dose	Route
1 and 3	Daunorubicin and Cytarabine (Vyxeos)	29 mg/m ² 65 mg/m ²	IV infusion

Cycle frequency

For patients who do not achieve remission with the first induction cycle a second induction cycle may be administered 2 to 5 weeks after the first if there is no unacceptable toxicity to Vyxeos.

The first consolidation cycle should be given 5 to 8 weeks after the start of the last induction cycle.

The second consolidation cycle should be given 5 to 8 weeks after the start of the first consolidation cycle in patients who do not show disease progression or unacceptable toxicity to Vyxeos.

Number of cycles

Treatment should be continued until as long as the patient continues to benefit, or until disease progression up to a maximum of 2 induction courses and 2 consolidation courses (4 cycles in total).

Administration

Vyxeos should be administered in 500mL sodium chloride 0.9% over 90 minutes. It should be administered via an infusion pump through a central venous catheter or a peripherally inserted central catheter. An in-line membrane filter may be used for the intravenous infusion of Vyxeos, provided the minimum pore diameter of the filter is greater than or equal to 15 µm. Following administration the line should be flushed with sodium chloride 0.9%.

Do not mix Vyxeos with, or administer as an infusion with, other medicinal products.

Central venous access should be used wherever possible. In urgent cases it may be necessary to start chemotherapy via a peripheral cannula until a central line can be arranged. **Do not administer Vyxeos via an intramuscular, intrathecal, or subcutaneous route.**

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.

Pre-medication

In case of hypersensitivity reactions, 60 minutes prior to infusion:

Chlorphenamine 10mg IV

Paracetamol 500mg-1g PO

Hydrocortisone 100mg IV

For patients with a high tumour burden premedication to reduce uric acid levels (with allopurinol or rasburicase) and pre hydration is recommended.

Emetogenicity

This regimen has moderate emetogenic potential.

Additional supportive medication

Allopurinol 300mg OD (100mg OD if CrCl < 20mL/min) for the first 14 days of initial induction chemotherapy. (If a remission is attained, subsequent use of allopurinol is not required).

Antifungal prophylaxis (as per local policy) daily from start of chemotherapy until end of neutropenia.

Antiviral prophylaxis as per local policy.

H₂ antagonist or PPI as per local policy.

Mouthwashes as per local policy.

Extravasation

Daunorubicin has been associated with local tissue necrosis at the site of medicinal product extravasation. Liposomal daunorubicin is classified as an exfoliant and cytarabine is neutral. 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.

Investigations – pre first cycle

Investigation	Validity period
FBC with film	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
LDH	7 days
Potassium	7 days
Magnesium	7 days
Calcium	7 days
Urate	7 days
Pregnancy test	7 days

Baseline ECG and echocardiogram recommended, especially if cardiac history, previous anthracycline exposure or other potential cardiac risk factors.

Recent bone marrow aspirate – this should be evaluated cytologically before proceeding with treatment.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC with film	7 days
U+Es (including creatinine)	7 days
LFTs	7 days

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	$\geq 1.0 \times 10^9/L$
Platelets	$\geq 100 \times 10^9/L$
CrCl	$\geq 30\text{mL/min}$
Bilirubin	$\leq 50 \mu\text{mol/L}$

Dose modifications

- **Haematological toxicity**

If neutrophils $< 1.0 \times 10^9/L$ and/or platelets $< 100 \times 10^9/L$ delay treatment until count recovery.

- **Renal impairment**

Dose adjustment is not required for patients with mild (CrCl 60 mL/min to 89 mL/min by Cockcroft Gault equation) 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.

- **Hepatic impairment**

Dose adjustment is not required for patients with a bilirubin level less than or equal to 50 $\mu\text{mol/L}$. There is no experience with Vyxeos in patients with hepatic impairment resulting in a bilirubin level greater than 50 $\mu\text{mol/L}$. Vyxeos should only be used in patients with severe hepatic impairment if the benefits outweigh the risks.

- **Other toxicities**

Acute copper toxicity - 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. Discontinue Vyxeos in patients with signs or symptoms of acute copper toxicity (combination of acutely abnormal LFTs and/or features of acute liver failure, headache, haemolysis, nausea and vomiting).

For any other toxicity grade ≥ 2 , discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression

Neutropenic sepsis

Cardiotoxicity

Hepatotoxicity

Serious hypersensitivity reactions including anaphylaxis

Infertility

Bleeding due to thrombocytopenia

- **Frequently occurring side effects**

Myelosuppression, infections

Skin rash

Constipation, diarrhoea

Stomatitis, mucositis

Nausea and vomiting

Anorexia

Arrhythmia

Headache, fatigue

Sleep disorders

Significant drug interactions – for full details consult product literature/ reference texts

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.

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.

Additional comments

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/m² have been associated with an increased incidence of treatment-induced congestive heart failure. This limit appears lower (400 mg/m²) 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.**

References

- Summary of product characteristics Vyxeos (Jazz Pharmaceuticals UK) Accessed 15 August 2019 via www.medicines.org.uk
- National Institute for Health and Clinical Excellence TA 552. Accessed 29 August 2019 via www.nice.org.uk
- AML 19 Trial Protocol, Version 7.0, Feb 2018

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