PIXANTRONE THERAPY

INDICATIONS FOR USE:

INDICATION	ICD10	Protocol Code
Monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy.	C85	00255a

ELIGIBILTY:

- Indication as above
- ECOG 0-2
- Life expectancy > 3months

EXCLUSIONS:

- Hypersensitivity to pixantrone dimaleate or to any of the excipients
- Immunisation with live virus vaccines
- Profound bone marrow suppression
- Severe abnormal hepatic function

USE with CAUTION:

Careful risk versus benefit consideration before receiving treatment with pixantrone should be undertaken in patients with

- Cardiac disease
- Risk factors such as a baseline LVEF value of < 45%
- Clinically significant cardiovascular abnormalities
- Myocardial infarction within the last 6 months
- Severe arrhythmia
- Uncontrolled hypertension, uncontrolled angina
- Prior cumulative doses of doxorubicin or equivalent exceeding 450 mg/m^2

TESTS:

Baseline tests: FBC, U&Es, LFTs, Cardiac function (LVEF)

Regular tests: FBC, U&Es & LFTs monthly
Cardiac function (LVEF) as clinically indicated

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Pixantrone is administered on day 1, 8 and 15 of a 28 day cycle for 6 cycles or until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route	Diluent & Rate
1,8,&15	Pixantrone	50mg/m^2	IV infusion	250ml NaCl 0.9% solution using a 0.2 micron in-line filter over a **minimum** of 60 mins
Recommended dose refers to the base of the active substance (pixantrone). Calculation of the individual dose to be administered to a patient must be based on the strength of the reconstituted solution that contains 5.8mg/ml pixantrone and the dose recommendation of 50 mg/m^2				
The amount in milligrams that is to be administered to a patient should be determined on the basis of the patient's body surface area (BSA). The BSA should be determined using the institutional standard for BSA calculation and should use a weight measured on day 1 of every cycle.				

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- The dose should be adjusted before the start of each cycle based on nadir haematologic counts or maximum toxicity from the preceding cycle of therapy.

Haematological:
Dose modification and the timing of subsequent doses should be determined by clinical judgement depending on the degree and duration of myelosuppression.
For subsequent courses, the prior dose can usually be repeated if white blood cell and platelet counts have returned to acceptable levels.

Day 1 of any cycle

IF ANC is < 1.0 x 10^9/L or platelet count is < 75 x 10^9/L it is recommended to delay treatment until ANC recovers to ≥ 1.0 x 10^9/L and platelet count to ≥ 75 x 10^9//L.

Table 1 shows the recommended guides to dosage adjustments based on haematological toxicity for for days 8 and 15 of the 28- day cycles

Table 1: Dose modifications for hematologic toxicity on days 8 and 15 of any cycle

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose Modification
LLN-1.0	and	LLN-50	No change in dose or schedule
< 1.0-0.5	or	< 50-25	Delay treatment until recovery to platelet count ≥ 50 x 10^9/L and ANC ≥ 1.0 x 10^9/ L.
<0.5	or	< 25	Delay treatment until recovery to platelet count ≥ 50 x 10^9/L and ANC ≥ 1.0 x 10^9/ L. Reduce the dose by 20%.

Renal impairment:

- Safety and efficacy has not been established in patients with impaired renal function.
- Patients with serum creatinine > 1.5 x ULN were excluded from the randomised study.
- Thus, pixantrone should be used with caution in patients with renal impairment.

Hepatic dysfunction:

- Safety and efficacy in patients with impaired hepatic function has not been established.
- Pixantrone should be used with caution in patients with mild or moderate liver impairment.
- It is not recommended for use in patients with severe excretory hepatic impairment

Table 2: Dose modification schedule based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Any grade 3 or 4 drug-related non cardiac toxicity other than nausea or vomiting		Delay treatment until recovery to grade 1. Reduce the dose by 20%.
Any grade 3 or 4 NYHA* cardiovascular toxicity or persistent LVEF decline		Delay treatment and monitor until recovery. Consider discontinuation for persistent decline in LVEF of ≥ 15% of baseline value.
* NYHA: New York Heart Association		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (**Refer to local policy).**

PREMEDICATIONS: None usually required

TAKE HOME MEDICATIONS:
Prophylaxis to prevent tumour lysis syndrome may be required in certain patients **(Refer to local policy)**.

OTHER SUPPORTIVE CARE:
No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.
The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Cardiotoxicity**: Changes in cardiac function including decreased LVEF or fatal congestive heart failure (CHF) may occur during or after treatment with pixantrone. Active or dormant cardiovascular disease, prior therapy with anthracyclines or anthracenediones, prior or concurrent radiotherapy to the mediastinal area, or concurrent use of other cardiotoxic medicinal products may increase the risk of cardiac toxicity. Cardiac toxicity with pixantrone may occur whether or not cardiac risk factors are present.
  Cardiac function should be monitored before initiation of treatment with pixantrone and periodically thereafter. If cardiac toxicity is demonstrated during treatment, the risk versus benefit of continued therapy with pixantrone must be evaluated.
- **Secondary malignancy:** The development of haematological malignancies such as secondary acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) is a recognised risk associated with anthracycline treatment and other topoisomerase II inhibitors. The occurrence of secondary cancers, including AML and MDS, may occur during or after treatment with pixantrone
- **Infection:** Pixantrone should not be administered to patients with an active, severe infection or in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose them to serious infection.
- **Tumour lysis syndrome:** Pixantrone may induce hyperuricaemia as a

consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells (tumour lysis syndrome) and can lead to electrolyte imbalances, which can result in kidney damage. Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after treatment in patients at high risk for tumour lysis (elevated LDH, high tumour volume, high baseline uric acid or serum phosphate levels). Hydration, urine alkalinisation, and prophylaxis with allopurinol or other agents to prevent hyperuricaemia may minimise potential complications of tumour lysis syndrome.

- **Patients on a sodium restricted diet**: This medicinal product contains approximately 1000 mg (43 mmol) sodium per dose after dilution. To be taken into consideration by patients on a controlled sodium diet

DRUG INTERACTIONS:

- No drug interactions have been reported in human subjects and no drug-drug interaction studies in humans have been performed.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Pixantrone - L01DB11

REIMBURSEMENT CATEGORY:

Pixantrone is funded through the PCRS managed Oncology Drug Management System (1/8/2015).

PRESCRIPTIVE AUTHORITY:

Consultant haematologist

REFERENCES:

1. Pettengell R, Coiffier B et al. Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial Lancet Oncol 2012;13(7) 696–706.
2. Engert, A et al. EXTEND PIX301: A Phase III Randomized Trial of Pixantrone Versus Other Chemotherapeutic Agents as Third-Line Monotherapy in Patients with Relapsed, Aggressive Non-Hodgkin's Lymphoma. Clin Lymph Myeloma 2006; 7 (2): 152 - 154.

3. Pixuvri ® Summary of Product Characteristics Accessed 7/5/15. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002055/WC500127968.pdf

Version	Date	Amendment	Approved By
1	01/10/15	Initial Draft	Dr CL Bacon

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