ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pixuvri 29 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains pixantrone dimaleate equivalent to 29 mg pixantrone

After reconstitution, each ml of concentrate contains pixantrone dimaleate equivalent to 5.8 mg pixantrone.

Excipient with known effect:
One vial contains 39 mg sodium.
Upon reconstitution and dilution, this medicinal product contains approximately 1g (43 mmol) sodium per dose, equivalent to 50% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
Dark blue lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pixuvri is indicated as 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.

4.2 Posology and method of administration

Pixuvri must be administered by physicians who are familiar with the use of antineoplastic agents and have the facilities for regular monitoring of clinical, haematological, and biochemical parameters during and after treatment (see section 6.6).

Posology

The recommended dose is 50 mg/m^2 of pixantrone on days 1, 8, and 15 of each 28-day cycle for up to 6 cycles.
Please note:
In the EU 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. In some trials and publications, the recommended dose is based on the salt form (pixantrone dimaleate)
However, the dose has to be adjusted before the start of each cycle based on nadir haematologic counts or maximum toxicity from the preceding cycle of therapy. The amount of Pixuvri 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.

Some caution is advised in obese patients as data on BSA- based dosing is very limited for this group.

Dose modification guidelines

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.

If on day 1 of any cycle the Absolute Neutrophil Count (ANC) is $< 1.0 \times 10^9$/l or platelet count is $< 75 \times 10^9$/l it is recommended to delay treatment until ANC recovers to $\geq 1.0 \times 10^9$/l and platelet count to $\geq 75 \times 10^9$/l.

Table 1 and Table 2 are recommended as guides to dosage adjustments 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

Grade	Platelet count	ANC count	Dose modification
1-2	LLN* – 50×10^9/l	LLN – 1.0×10^9/l	No change in dose or schedule.
3	$< 50 – 25 \times 10^9$/l	$< 1.0 – 0.5 \times 10^9$/l	Delay treatment until recovery to platelet count $\geq 50 \times 10^9$/l and ANC** $\geq 1.0 \times 10^9$/l.
4	$< 25 \times 10^9$/l	$< 0.5 \times 10^9$/l	Delay treatment until recovery to platelet count $\geq 50 \times 10^9$/l and ANC** $\geq 1.0 \times 10^9$/l. Reduce the dose by 20%.

* LLN: Lower Limit of the Normal range
** ANC: Absolute Neutrophil Count

Table 2
Treatment modifications for non-hematologic toxicities

Toxicity	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 $\geq$ 15% of baseline value.

* NYHA: New York Heart Association
** LVEF: Left Ventricular Ejection Fraction

<u>*Special populations*</u>
Paediatric population
The safety and efficacy of Pixuvri in children aged < 18 years has not yet been established. No data are available.

Elderly
No specific dose adjustment is required in elderly patients (aged $\geq$ 65 years).

Renal impairment
The safety and efficacy of Pixuvri has not been established in patients with impaired renal function. Patients with serum creatinine > 2 x Upper Limit of the Normal range (ULN) were excluded from the randomised studies. Thus, Pixuvri should be used with caution in patients with renal impairment.

Patients with impaired hepatic function
The safety and efficacy of Pixuvri in patients with impaired hepatic function has not been established. Pixuvri should be used with caution in patients with mild or moderate liver impairment. Pixuvri is not recommended for use in patients with severe excretory hepatic impairment, (see section 4.3).

Patients with poor performance status
There is currently no information on the safety and efficacy of patients with poor performance status (ECOG > 2). Caution should be exercised when treating such patients.

Method of administration

Pixuvri is for intravenous use only. The safety of intrathecal use has not been established.

Pixuvri is intended for administration as a slow intravenous infusion using an in-line filter (over a minimum of 60 minutes) only after reconstitution with 5 ml sodium chloride 9 mg/ml (0.9%) solution for injection and after further dilution with sodium chloride 9 mg/ml (0.9%) solution for injection to a final volume of 250 ml.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to pixantrone dimaleate, or to any of the excipients listed in section 6.1
- Immunisation with live virus vaccines
- Profound bone marrow suppression
- Severe abnormal hepatic function.

4.4 Special warnings and precautions for use

All initial treatment with Pixuvri should be preceded by a careful baseline assessment of blood counts, serum levels of total bilirubin, serum levels of total creatinine, and cardiac function as measured by left ventricular ejection fraction (LVEF).

Myelosuppression
Severe myelosuppression may occur. Patients treated with Pixuvri are likely to experience myelosuppression (neutropenia, leukopenia, anaemia, thrombocytopenia, and lymphopenia) with the predominant manifestation being neutropenia. With the recommended dose and schedule, neutropenia is usually transient, reaching its nadir on days 15-22 following administration on days 1, 8, and 15 with recovery usually occurring by day 28.

Careful monitoring of blood counts is required, including leukocyte, red blood cells, platelet, and absolute neutrophil counts. Recombinant hematopoietic growth factors may be used according to institutional or European Society for Medical Oncology (ESMO) guidelines. The dose modifications should be considered (see section 4.2).

Cardiotoxicity
Changes in cardiac function including decreased LVEF or fatal congestive heart failure (CHF) may occur during or after treatment with Pixuvri.

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 Pixuvri may occur whether or not cardiac risk factors are present.

Patients with cardiac disease or risk factors such as a baseline LVEF value of < 45% by multigated radionuclide (MUGA) scan, clinically significant cardiovascular abnormalities (equal to New York Heart Association [NYHA] grade 3 or 4), myocardial infarction within the last 6 months, severe arrhythmia, uncontrolled hypertension, uncontrolled angina, or prior cumulative doses of doxorubicin or equivalent exceeding 450 mg/m^2 should receive careful risk versus benefit consideration before receiving treatment with Pixuvri.

Cardiac function should be monitored before initiation and during the treatment with Pixuvri . If cardiac toxicity is demonstrated during treatment, the risk versus benefit of continued therapy with Pixuvri 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 Pixuvri.

Infection
Infections, including pneumonia, cellulitis, bronchitis, and sepsis have been reported during clinical trials (see section 4.8). Infections have been associated with hospitalisation, septic shock, and death. Patients with neutropenia are more susceptible to infections, although, in the clinical studies there was no increased incidence of atypical, difficult-to-treat infections, such as systemic mycotic infections or infections with opportunistic organisms such as *Pneumocystis jiroveci*.

Pixuvri 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.

Immunisation
Immunisation may be ineffective when given during Pixuvri therapy. Immunisation with live virus vaccines is contraindicated due to the immunosuppression associated with Pixuvri therapy (see section 4.3).

Extravasation
If extravasation occurs the administration should be stopped immediately and restarted in another vein. The non-vesicant properties of Pixuvri minimise the risk of local reaction following extravasation.

Prevention of photosensitivity reactions
Photosensitivity is a potential risk based on *in vitro* and in vivo non-clinical data. One case of photosensitivity reaction has been reported in the clinical trial program considered as non-serious and with outcome recovered. As a precaution, patients should be advised to follow sun protection strategies, including wearing sun protective clothing and using sunscreen. Since most medicinal product-induced photosensitivity reactions are caused by wavelengths within the UV-A range, sunscreen that strongly absorbs UV-A is recommended.

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.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interactions have been reported in human subjects and no drug-drug interaction studies in humans have been performed.

In vitro inhibition studies
*In vitro s*tudies with the most common human cytochrome P450 isoforms (including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) have shown a possible mixed-type inhibition of CYP1A2 and CYP2C8 that may be of clinical relevance. No other significant clinically relevant interactions with CYPP450s were observed.

Theophylline: when co-administering the narrow-therapeutic index medicinal product theophylline, which is primarily metabolised by CYP1A2, there is a theoretical concern that this substrate may

increase in concentration resulting in theophylline toxicity. Theophylline levels should be carefully monitored in the weeks immediately following initiation of Pixuvri concurrent therapy.

Warfarin is partially metabolised by CYP1A2, therefore, a theoretical concern exists with regard to co-administration of this medicinal product and the effect inhibition of its metabolism might have on its intended action. Coagulation parameters, specifically international normalised ratio (INR), should be monitored in the days immediately following the initiation of Pixuvri concurrent therapy.

Amitriptyline, haloperidol, clozapine, ondansetron and propranolol are metabolised by CYP1A2, and therefore, a theoretical concern exists that co-administration of Pixuvri may increase blood levels of this medicinal product.

Although a risk to inhibition of pixantrone towards CYP2C8 could not be ascertained, caution should be observed when co-administering substances that are primarily metabolised via CYP2C8, such as *repaglinide, rosiglitazone, or paclitaxel* e.g. by careful monitoring for side effects.

Based on *in vitro* studies, pixantrone was found to be a substrate for the membrane transport proteins P-gp/BRCP and OCT1 and agents which inhibit these transporters have the potential to decrease hepatic uptake and excretion efficiency of pixantrone. Blood counts should be closely monitored when co-administered with agents which inhibit such transporters such as cyclosporine A or tacrolimus, commonly used to control chronic graft-versus-host disease, and the anti-HIV agents ritonavir, saquinavir, or nelfinavir.

In addition, caution should be taken when pixantrone is continuously co-administered with efflux transport inducers such as rifampicin, carbamazepin and glucocorticoids, as pixantrone excretion might be increased with a consequent decrease of systemic exposure.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential and their partners should be advised to avoid pregnancies.

Women and men must use effective contraception during and up to 6 months after treatment.

Pregnancy
There are no data from the use of pixantrone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Pixuvri is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether Pixuvri/metabolites are excreted in human milk.

A risk to the newborn/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with Pixuvri.

Fertility
After repeated administrations of Pixuvri at doses as low as 0,1 mg/kg/day, a dose-dependent testicular atrophy was detected in the dogs. This effect has not been evaluated in humans. As with other agents in the general class of deoxyribonucleic acid (DNA) damaging agents, Pixuvri may be associated with fertility impairment. Whilst the effect on fertility has not been ascertained, a precaution will be to advise male patients to use contraceptive methods (preferably barrier) during treatment and for a period of 6 months post-treatment to allow new sperm to mature. To avoid the risk of long term infertility, sperm banking should be considered.

4.7 Effects on ability to drive and use machines

It is not known whether Pixuvri has an effect on the ability to drive a car or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common toxicity is bone marrow suppression, particularly of the neutrophil lineage. Although the incidence of severe marrow suppression with clinical consequences is relatively low, patients have been treated with Pixuvri were closely monitored by frequent blood counts, particularly for neutropenia. The incidence of severe infections was low and opportunistic infections associated with immunocompromise were not seen. Although the occurrence of cardiac toxicity manifested by CHF appears to be lower than that would be expected with related medicinal products such as anthracyclines, monitoring of LVEF either by MUGA scans or ECHO is recommended to assess subclinical cardiotoxicity. Experience with pixantrone is limited to patients with LVEF ≥ 45% with most patients having values ≥ 50%. Experience administering Pixuvri to patients with more significant cardiac compromise is limited and should only be undertaken in the context of a clinical trial. Other toxicities such as nausea, vomiting, and diarrhoea were generally infrequent, mild, reversible, manageable, and expected in patients treated with cytotoxic agents. Effects on hepatic or renal function were minimal.

Tabulated list of adverse reactions

Adverse drug reactions (ADR) reported with Pixuvri are from final data from all completed single agent studies (n=197). ADRs are listed in Table 3 below by MedDRA system organ class and by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3
Adverse drug reactions reported related to Pixuvri in completed Pixuvri single agent studies by frequency

System Organ Class	Frequency	Undesirable effect
Infections and infestations	*Common*	Neutropenic infection, respiratory tract infection, infection, sepsis
	Uncommon	Bronchitis, candidiasis, cellulitis, herpes zoster, meningitis, nail infection, oral fungal infection, oral herpes, pneumonia, salmonella gastroenteritis, septic shock
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	*Uncommon*	Neoplasm progression Secondary malignancy (including reports of AML and MDS)
Blood and lymphatic system disorders*	*Very common*	Neutropenia, leukopenia, lymphopenia, anaemia, thrombocytopenia
	Common	Febrile neutropenia, blood disorder
	Uncommon	Bone marrow failure, eosinophilia
Immune system disorders	*Uncommon*	Hypersensitivity to the medicinal product
Metabolism and nutrition disorders	*Common*	Anorexia, hypophosphataemia
	Uncommon	Hyperuricaemia, hypocalcaemia, hyponatraemia,
Psychiatric disorders	*Uncommon*	Anxiety, insomnia, sleep disorder
Nervous system disorders	*Common*	Taste disturbances, paraesthesia, headache, somnolence
	Uncommon	Dizziness, lethargy
Eye disorders	*Common*	Conjunctivitis
	Uncommon	Dry eye, keratitis

Table 3 Adverse drug reactions reported related to Pixuvri in completed Pixuvri single agent studies by frequency		
System Organ Class	**Frequency**	**Undesirable effect**
Ear and labyrinth disorders	*Uncommon*	Vertigo
Cardiac disorders*	*Common*	Left ventricular dysfunction, cardiac disorder, cardiac failure congestive, bundle branch block, tachycardia
	Uncommon	Arrhythmia
Vascular disorders	*Common*	Pallor, vein discolouration, hypotension
	Uncommon	Vein disorder
Respiratory, thoracic and mediastinal disorders	*Common*	Dyspnoea, cough
	Uncommon	Pleural effusion, pneumonitis, rhinorrhoea
Gastrointestinal disorders	*Very common*	Nausea, vomiting
	Common	Stomatitis, diarrhoea, constipation, abdominal pain, dry mouth, dyspepsia,
	Uncommon	Esophagitis, oral paresthesia, rectal haemorrhage
Hepatobiliary disorders	*Uncommon*	Hyperbilirubinaemia, hepatotoxicity
Skin and subcutaneous tissue disorders*	*Very common*	Skin discolouration, alopecia
	Common	Erythema, nail disorder, pruritus
	Uncommon	Night sweats, petechiae, rash macular, skin ulcer
Musculoskeletal and connective tissue disorders	*Common*	Bone pain
	Uncommon	Arthralgia, arthritis, back pain, muscular weakness, musculoskeletal chest pain, musculoskeletal stiffness, neck pain, pain in extremity
Renal and urinary disorders	*Very common*	Chromaturia
	Common	Proteinuria, haematuria
	Uncommon	Oliguria
Reproductive system and breast disorders	*Uncommon*	Spontaneous penile erection
General disorders and administration site conditions	*Very common*	Asthenia
	Common	Fatigue, mucosal inflammation, pyrexia, chest pain, oedema
	Uncommon	Chills, injection site coldness, local reaction
Investigations	*Common*	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased
	Uncommon	Bilirubin urine, blood phosphorus increased, blood urea increased, gamma-glutamyltransferase increased, neutrophil count increased, weight decreased

** ADRs discussed below*

Description of selected adverse reactions

Hematologic toxicities and complications of neutropenia

Hematologic toxicities have been the most frequent toxicity observed but they have, in general, been easily managed with granulocyte-colony stimulating factor (G-CSF) and transfusion support as needed. While grade 3-4 neutropenia occurred in randomised trials more frequently among Pixuvri recipients, they were uncomplicated in the majority of cases, noncumulative and associated with a low incidence of

febrile neutropenia or infections, none leading to fatal outcome. Importantly, growth factor support was not routinely required and transfusions with red blood cells and platelets were uncommon. (See section 4.4)

Cardiac toxicity
In the study PIX 301, decreased ejection fraction occurred in 13 patients (19.1%) in the Pixuvri group. In 11 Pixuvri-treated patients, these events were grade 1-2 and in 2 patients they were grade 3; these events were transient and not Pixuvri dose related. Cardiac failure events (MedDRA terms cardiac failure, cardiac failure acute and cardiac failure congestive) occurred in 6 patients (8.8%) treated with Pixuvri (2 patients with grade 1-2, 1 patient with grade 3, and 3 patients, 2 considered as unrelated, with grade 5). Three Pixuvri patients (4.4%) had tachycardia, arrhythmia, sinus tachycardia, supraventricular tachycardia or bradycardia. Most patients had received prior doxorubicin or equivalent at dose of up to 450 mg/m².
A baseline cardiac evaluation with a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiac toxicity. Repeated MUGA scan or ECHO determinations of LVEF should be considered in patients with risk factors such as high cumulative exposure to prior anthracyclines or significant pre-existing cardiac disease. (See section 4.4)

Other common toxicities
Skin discolouration and chromaturia are known related effects of Pixuvri administration due to the colour of the compound (blue). The skin discolouration generally disappears over a few days to weeks as the medicinal product is cleared.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national system listed in Appendix V.

4.9 Overdose

In the clinical trial program, there has been one report of overdose with Pixuvri with no reported concomitant adverse events.

Single doses of pixantrone up to 158 mg/m^2 have been given in dose-escalation clinical trials without evidence of dose-related toxicity.

If overdose occurs, supportive management is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, anthracyclines, and related substances.
ATC code: L01DB11

Mechanism of action
The active substance of Pixuvri is pixantrone , a cytotoxic aza-anthracenedione.

Unlike approved anthracyclines (doxorubicin and others) and anthracenediones (mitoxantrone), pixantrone is only a weak inhibitor of topoisomerase II. Moreover, unlike anthracyclines or anthracenediones, pixantrone directly alkylates DNA forming stable DNA adducts and cross-strand breaks. Furthermore, because it incorporates a nitrogen heteroatom into the ring structure and does not have ketone groups, pixantrone has less potential for generating reactive oxygen species, binding iron, and forming alcohol metabolites that are felt to cause the cardiac toxicity of anthracyclines. Due to this unique structure, pixantrone produced minimal cardiotoxicity in animal models compared with doxorubicin or mitoxantrone.

A comprehensive retrospective population PK/PD analysis of Phase 1 trials and combination regimens (Phase 1/2) demonstrated that progression-free survival and Grade 2-3 neutropenia were related to Pixuvri exposure.

Clinical efficacy and safety

The safety and efficacy of Pixuvri as single-agent therapy were evaluated in a multicentre, randomised, active controlled trial in patients with relapsed or refractory aggressive NHL after receiving at least two prior therapies. This study randomised 140 patients (1:1) to treatment with either Pixuvri or to an investigator chosen single-agent chemotherapy on the comparator arm. Patient demographics and baseline disease characteristics were well balanced between the treatment groups, and no statistically significant differences were noted. For the study overall, patient median age was 59, 61% were male, 64% were Caucasian, 76% had Ann Arbor stage III/IV disease at baseline, 74% had a baseline International Prognostic Index (IPI) score ≥ 2, and 60% had received ≥ 3 prior chemotherapies. Mantle cell lymphoma patients were not included in the pivotal study. Patients in PIX 301 were required to have been sensitive to prior anthracycline therapy (confirmed or unconfirmed CR or PR).

There is limited data in patients previously treated with rituximab (38 patients in the Pixuvri arm and 39 patients in the comparator arm).

Tumour response was assessed by a blinded independent central review panel according to the international workshop to standardise response criteria for NHL. Patients treated with Pixuvri showed a significantly higher rate of complete responses and unconfirmed complete responses (CR/CRu), and a higher objective response rate (ORR), compared to the comparator group (see Table 4).

Table 4
Summary of response per independent assessment panel (ITT population)

	End-of-Treatment			**End-of-Study**		
	Pixuvri (n=70)	**Comparator** (n=70)	**P-value**	**Pixuvri** (n=70)	**Comparator** (n=70)	**P-value**
CR/CRu	14 (20.0%)	4 (5.7%)	0.021	17 (24.3%)	5 (7.1%)	0.009
CR	8 (11.4%)	0 (0%)		11 (15.7%)	0 (0.0%)	
CRu	6 (8.6%)	4 (5.7%)		6 (8.6%)	5 (7.1%)	
ORR (CR, Cru, and PR)	26 (37.1%)	10 (14.3%)	0.003	28 (40.0%)	10 (14.3%)	0.001
The Fisher exact test was used to compare proportions in the Pixuvri and comparator chemotherapeutic groups.						

Patients treated with Pixuvri demonstrated 40% improvement in progression-free-survival compared to patients treated with comparator agents with 2.7 months longer median PFS (hazard ratio (HR)=0.60, logrank p=0.005) (see Figure 1 below).

The median overall survival for patients treated with Pixuvri was 2.6 months longer compared to patients treated with comparator (HR=0.79, logrank p=0.25) (see Figure 2 below).

Figure 1
PIX301 Progression-free survival - end of study

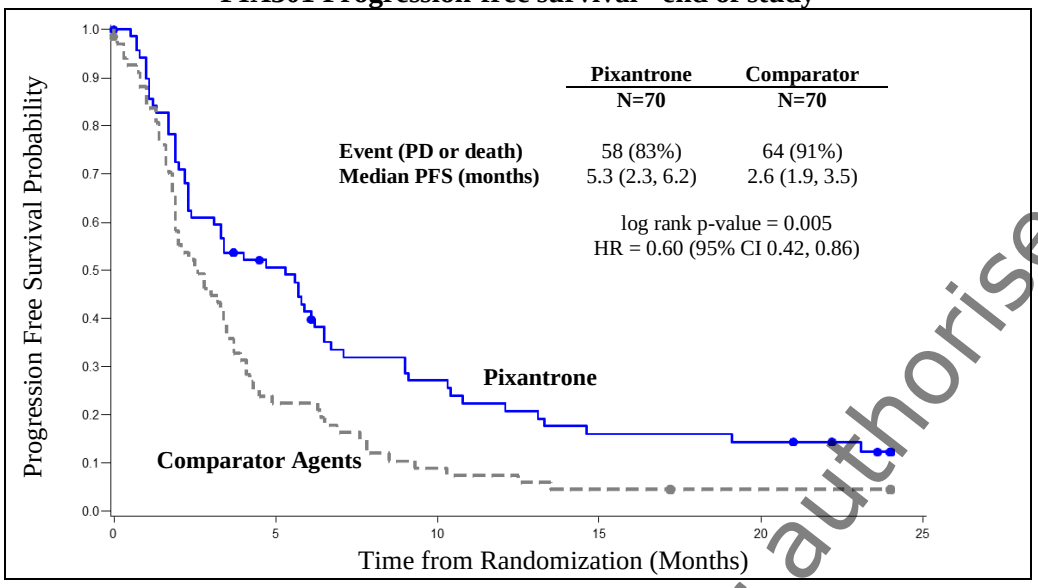
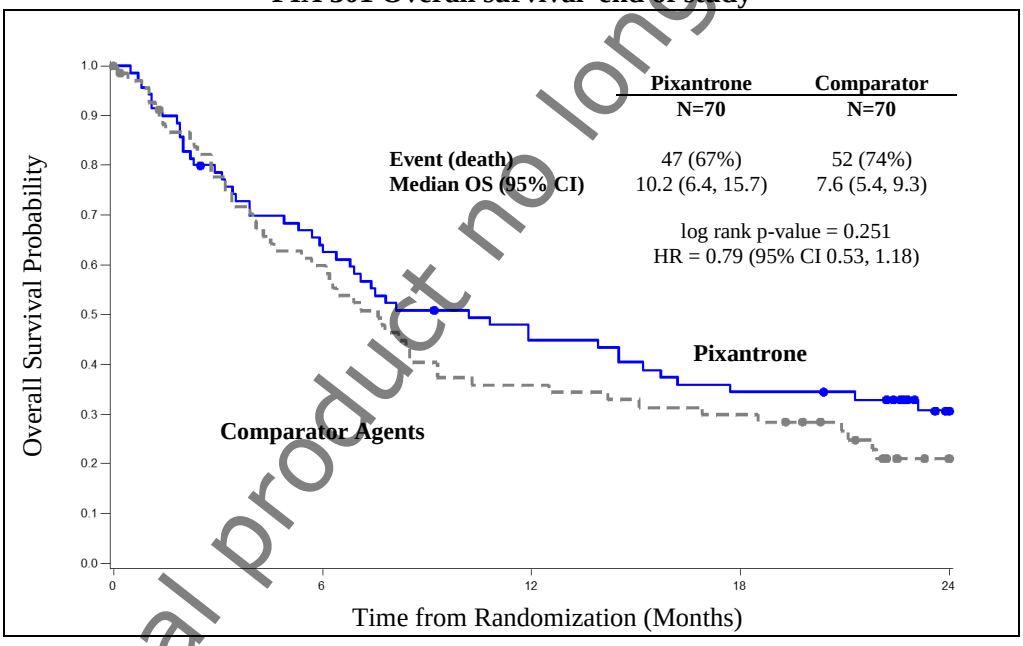


Figure 2
PIX 301 Overall survival–end of study



The results in the rituximab pretreated patients still showed superior treatment benefit with Pixuvri over the comparator for overall response rate (31.6% with Pixuvri versus 17.9% with the comparator) and median progression-free survival (3.3 months with Pixuvri versus 2.5 months with the comparator). However, the benefit of Pixuvri has not been established when used as fifth line or greater in patients refractory to last therapy, and there is very limited data in this group of patients.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Pixuvri in all subsets of the paediatric population in treatment of non-Hodgkin lymphoma. (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following intravenous administration, plasma concentrations of pixantrone reached the maximal concentration at the end of infusion and then declined poly-exponentially. The pharmacokinetics of Pixuvri was dose-independent in the 3 mg/m^2 to105 mg/m^2 dose range and no substantial differences were observed when the medicinal product was given as a single agent or in combination studies. Average exposures as single agent accounted for:

Pixuvri Dose (mg/m^2)	Number of patients	AUC (0-24h) (ng.hr/ml)
33	3	982 ± 115
49	6	1727 ± 474
88	2	3811

From an analysis of population PK data, for a target recorded dose of 50 mg/m^2 of pixantrone the median 28-day cycle exposure was 6320 ng.hr/ml (90% CI, 5990-6800 ng.hr/ml), for 3 doses / 4 week cycle.

Distribution
Pixuvri has a large volume of distribution of 25.8 l and is approximately 50% bound to plasma proteins.

Biotransformation
Acetylated metabolites are the major biotransformation products of pixantrone. However, *in vitro*, conversion of pixantrone into the acetylated metabolites by either NAT1 or NAT2 was very limited. In human urine, the compound was mainly excreted unchanged, and very small amounts of phase I and phase II acetylated metabolites were found. Therefore, metabolism does not appear to be an important elimination pathway for pixantrone. Acetylated metabolites were pharmacologically inactive and metabolically stable.

Elimination
Pixantrone has a moderate to high total plasma clearance of 72.7 l/hr and a low renal excretion accounting for less than 10% of the administered dose in 0-24 hours. The terminal half-life ranged from 14.5 to 44.8 hr with a mean of 23.3 ± 8.0 (n=14, CV=34%) and a median of 21.2 hr. Due to the limited contribution of renal clearance, plasma clearance is mainly non-renal. Pixuvri may be metabolised in the liver and/or excreted in the bile. As metabolism appears to be limited, biliary excretion of unchanged pixantrone may be the major elimination pathway. Hepatic clearance approximates the hepatic plasma flow, suggesting a high hepatic extraction ratio and, therefore, efficient parent active substance elimination. Hepatic uptake of pixantrone is possibly mediated by OCT1 active transporters and biliary excretion by P-gp and BCRP.

Pixantrone had only a weak or no capability to inhibit P-gp, BCRP, and BSEP transport mechanism *in vitro*.

Pixantrone did inhibit OCT1-mediated metformin transport *in vitro*, but is not expected to inhibit OTC1 *in vivo* at clinically relevant concentrations.

Pixantrone was a poor inhibitor of OATP1B1 and OATP1B3 uptake transporters *in vitro*.

Linearity/non-linearity
Pharmacokinetics of pixantrone proved to be linear in a broad range of doses, from 3 mg/m^2 to 105 mg/m^2.

Pharmacokinetic/pharmacodynamic relationship(s)
A relationship between plasma exposure to pixantrone and neutrophil count has been observed.

5.3 Preclinical safety data

After a single intravenous administration of Pixuvri at 29 mg/kg and 38 mg/kg, immediate deaths were seen in mice (114 mg/m^2, LD10). Decreases in white and red blood cells and alterations in bone marrow, spleen, kidney, and testes were observed. Similar findings were reported in rats, and in dogs at 116 mg/m^2. In dogs, tachycardia and electrocardiography (ECG) changes occurred immediately after treatment.

In repeated-dose studies in mice, rats, and dogs, the main findings were myelotoxicity, nephrotoxicity (except dogs), and testicular damage.

In dogs, Pixuvri given at 0.5 to 0.9 mg/kg for six cycles did not cause mortality or severe clinical signs, including ECG or body weight changes. Males were more sensitive to treatment, with respect to reduction in white blood cells and platelet count (reversible) and lymphoid depletion (spleen and thymus), as well as the marked toxicity to reproductive organs, as expected from a cytotoxic agent. Except for a transient increase in exposure in females after the third cycle, there were no marked differences in pharmacokinetic parameters. Males showed, however, slightly higher exposure than females.

In dogs, the heart was not affected by treatment, as no ECG changes were seen at different treatment times, nor heart changes were detected at gross- and histopathology. Kidney function and histology were similarly not affected both in 4- and 26-week studies.

The cardiotoxic potential of Pixuvri compared with equiactive doses of doxorubicin and mitoxantrone in treatment-naïve and doxorubicin-pre-treated mice was evaluated. Pixantrone dimaleate up to 27 mg/kg given twice a week for 4 weeks did not induce any cardiotoxic effects, while mitoxantrone, as expected, was cardiotoxic at all tested doses (0.6, 1.6, and 1.5 mg/kg). Slight nephropathy was induced by Pixuvri. Minimal cardiotoxicity of Pixuvri was also demonstrated with repeat treatment cycles at the same doses.

Genotoxicity studies confirmed the potential for clastogenic effects in mammalian cells *in vitro* and *in vivo*. Pixuvri was mutagenic in the Ames test, increased the number of chromosomal aberrations in human lymphocytes, and increased the frequency of micronuclei *in vivo*.

Pixuvri caused maternal and foetal toxicity in rats and rabbits, even at a dose as low as 1.8 mg/kg given on days 9-11 of pregnancy, higher doses resulting in abortions and total embryo resorption. Embryotoxicity was characterised by reduced mean foetal weight, foetal malformations and incomplete or delayed foetal ossification. No long-term animal studies have been performed to establish the carcinogenic potential of Pixuvri. No local tolerance study was conducted.

Pixuvri has been shown to cause phototoxic effects on 3T3 cells *in vitro*.

In a colony-forming units study in mice, the myelotoxicity of Pixuvri and mitoxantrone administered at their LD10 (pixantrone dimaleate 38 mg/kg and mitoxantrone 6.1 mg/kg) was similar.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Lactose monohydrate
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
5 years

Reconstituted and diluted solution
Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (15°C to 25°C) and daylight exposure in polyethylene (PE) standard infusion bags.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with grey butyl rubber stopper with aluminium seal and red plastic cap containing 50 mg pixantrone dimaleate equivalent to 29 mg pixantrone.
Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Reconstitution and dilution
Aseptically reconstitute each 29 mg vial with 5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. The lyophilised powder should completely dissolve in 60 seconds with agitation. This yields a dark blue solution with a pixantrone concentration of 5.8 mg/ml.

Aseptically withdraw the volume needed for the required dose (based on 5.8 mg/ml concentration) and transfer to a 250 ml infusion bag of sodium chloride 9 mg/ml (0.9%) solution for injection. The final concentration of pixantrone in the infusion bag should be less than 580 microgram /ml based upon input of reconstituted medicinal product. Compatibility with other diluents has not been determined. After transferring, thoroughly mix the contents of the infusion bag. The mixture should be a clear and dark blue solution.

Polyethersulfone 0.2 µm pore size in-line filters should be used during administration of the diluted Pixuvri solution.

Pixuvri is a cytotoxic agent. Avoid contact with eyes and skin. Use gloves, masks, and protective eyewear when handling Pixuvri and during decontamination procedures.

Special precautions for disposal
Pixuvri is for single use only. Any unused medicinal product or waste material including materials used for reconstitution, dilution, and administration should be disposed of in accordance with local requirements applicable to cytotoxic agents.

7. MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/764/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 May 2012
Date of latest renewal: 06 June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Les Laboratoires Servier Industrie
905 Route de Saran
45520 Gidy
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Pixuvri 29 mg powder for concentrate for solution for infusion
pixantrone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains pixantrone dimaleate equivalent to 29 mg pixantrone. After reconstitution, each ml of concentrate contains pixantrone dimaleate equivalent to 5.8 mg pixantrone.

3. LIST OF EXCIPIENTS

Lactose monohydrate, sodium chloride, hydrochloric acid, sodium hydroxide. Contains sodium, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
Pack size of 1 vial.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Reconstitute and dilute before use.
Read the package leaflet before use.
For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: Handle with caution.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/764/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL

1. NAME OF THE MEDICINAL PRODUCT

Pixuvri 29 mg powder for concentrate for solution for infusion
pixantrone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains pixantrone dimaleate equivalent to 29 mg pixantrone. After reconstitution, each ml of concentrate contains pixantrone dimaleate equivalent to 5.8 mg pixantrone.

3. LIST OF EXCIPIENTS

Lactose monohydrate, sodium chloride, hydrochloric acid, sodium hydroxide. Contains sodium, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Reconstitute and dilute before use.
Read the package leaflet before use.
For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic. Handle with caution.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/764/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Pixuvri 29 mg powder for concentrate for solution for infusion
pixantrone

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effect, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pixuvri is and what it is used for

Pixuvri belongs to a pharmacotherapeutic group of medicines known as 'antineoplastic agents'. These are used to treat cancer.

Pixuvri is used for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin Lymphomas. Pixuvri kills cancer cells by binding to DNA, resulting in cell death. It is used for patients whose cancer does not respond or has returned after they have received other chemotherapy treatments.

2. What you need to know before you use Pixuvri

Do not use Pixuvri
- if you are allergic to pixantrone dimaleate or any of the other ingredients of this medicine (listed in section 6).
- if you have recently received a vaccine.
- if you have been told that you have persistent, long-term low numbers of red blood cells, white blood cells, and platelets.
- if you have very severe liver problems.

Warnings and precautions
Talk to your doctor before using Pixuvri:

- if you have been told that your white blood cell count is very low.
- if you have heart disease or uncontrolled high blood pressure, especially if you have ever been told you had heart failure or if you have had a heart attack within the last six months.
- if you have an infection.
- if you have ever been treated for cancer.
- if you follow a specific sodium restricted diet.
- if you are taking other medicines which could interact with Pixuvri (see 'Taking other medicines' below).

Skin sensitivity to sunlight

During treatment with pixantrone, you should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment). If you will be exposed to sunlight, you should wear sun-protective clothing and use sunscreen that strongly absorbs UV-A.

Children and adolescents
Do not give this medicine to children under the age of 18 years because there is no information about Pixuvri treatment in children and adolescents.

Other medicines and Pixuvri
Tell your doctor if you are taking, have recently taken or might take any other medicines. This is extremely important as using more than one medicine at the same time can strengthen or weaken their effect. Pixuvri must not be used with other medicines unless your doctor has told you it is safe to do so.
In particular, make sure to tell your doctor if you are currently using, or have recently used, any of the following medicines:

Tell your doctor if you take medicines such as:

- Warfarin to prevent blood clot formation
- Theophylline to treat lung conditions like emphysema or asthma
- Amitriptyline to treat depression
- Olanzapine, Clozapine to treat schizophrenia or maniac depression
- Haloperidol to treat anxiety and sleeplessness
- Ondansetron to prevent nausea and vomiting during chemotherapy
- Propranolol to treat high blood pressure

Pixuvri with food and drink
You do not have to change your diet after treatment with Pixuvri unless instructed by your doctor.

Pregnancy, breast-feeding and fertility
Pixuvri must not be given to pregnant women as it may cause harm to unborn babies. If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine.

Adequate contraceptive precautions must be used when receiving Pixuvri and for up to 6 months after treatment. This applies to women who can become pregnant and men receiving Pixuvri who may be able to father a child.

Do not breast-feed while you are being treated with Pixuvri.

Driving and using machines
It is not known whether Pixuvri has an effect on your ability to drive a car or use machines.

Pixuvri contains sodium
Upon reconstitution and dilution, this medecine contains approximately 1g (43 mmol) sodium (main component of cooking salt) per dose. This is equivalent to 50% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Pixuvri

How much of Pixuvri is given
The amounts (dose) of Pixuvri that will be given to you will depend on your body surface area in square meters (m^2). This is determined by your height and weight. The results of blood tests and your medical condition will also be taken into account. The recommended dose is 50 mg/m^2. If necessary, your doctor will adjust the dose during treatment.

Your doctor will carry out some tests before you are given Pixuvri.

How often Pixuvri is given
Pixuvri is given on days 1, 8, and 15 of each 28-day cycle for up to 6 cycles.

Before the infusion is administered you may be given medicines to prevent or reduce possible reactions to Pixuvri, such as medicines to prevent sickness.

How Pixuvri is given
Pixuvri is given through a drip into a vein (by intravenous infusion). This will be done by a nurse or doctor.

How long the infusion will take
This will take approximately one hour unless otherwise stated.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Infusion reactions
Pain/redness of the injection site may occur rarely during infusion of Pixuvri. Tell the person giving you the infusion immediately if you feel pain or if the injection site gets red. The infusion may need to be slowed down or stopped. When these symptoms go away or improve, the infusion can be continued.

Pixuvri has a deep blue colour and for several days after receiving Pixuvri, your skin and eyes may develop a bluish discolouration, and your urine may have a bluish discolouration. The skin discolouration generally disappears over a few days to weeks as the drug is cleared.

Infections
Tell your doctor if you get any symptoms of an infection (for example, fever, chills, trouble breathing, cough, sores in your mouth, trouble swallowing, or severe diarrhoea) after Pixuvri treatment. You might get infections more easily after you have been given Pixuvri.

Heart
There is a possibility that your heart pumping function could decrease as a result of the treatment or you might even develop a serious condition called heart failure, especially if your heart function was already compromised at the beginning of the treatment with Pixuvri. Your doctor will monitor your heart function if there is any sign or symptom of your heart being affected.

Tell your doctor if you think you have any of the following reactions

Very common: may affect more than 1 in 10 people
- nausea, vomiting
- skin discolouration
- thinning or loss of hair
- abnormal colouration of the urine
- physical weakness
- low number of white blood cells, low number of red blood cells (anaemia), and low number of platelets in the blood (may require transfusion).

Common: may affect up to 1 in 10 people
- infection such as lung infection, skin infections, infections with low white blood cells, thrush
- fever
- severe blood infection (sepsis)

- taste disturbances
- abnormal sensations of the skin such as numbness, tingling, pricking (paraesthesia)
- headache
- sleepiness
- tiredness
- inflammation of the eyes (conjunctivitis)
- diarrhoea
- pain in the abdomen
- inflammation and/or ulceration of the throat and the mouth
- dry mouth, constipation, indigestion, loss of appetite
- skin changes such as redness and itching of the skin, nail changes
- damage to the heart, decrease in heart's ability to pump blood, blockage of electrical signals in your heart, uneven or fast heartbeat.
- low blood pressure
- vein discolouration, pale skin
- shortness of breath, cough
- blood in urine
- excess protein in urine
- swelling of legs or ankles or other parts of the body
- bone pain
- chest pain
- low levels of phosphate in the blood
- abnormal blood test for liver or kidney function.

Uncommon: may affect up to 1 in 100 people
- severe infections such as septic shock, bronchitis, pneumonia, candidiasis, cellulitis, meningitis, gastroenteritis
- viral infections such as shingles or reactivation of other virus such as herpes in the mouth
- nervousness, sleeplessness
- loss of energy
- dizziness, vertigo
- dryness of the eye
- numbness of the mouth
- infection of the cornea
- allergy to the medicine
- decrease in blood calcium and sodium level; increase in blood uric acid level
- inflammation or fluid accumulation around the lungs
- runny nose
- bleeding such as gut bleed, purple spots on body due to broken blood vessels
- vein irritation
- night sweats
- irregular heartbeat
- spontaneous erection
- skin rash and/or ulceration
- pain, swelling, weakness, stiffness in joints or muscles
- decreased urinary output
- loss of weight
- increased bilirubin in blood or urine
- inflammation of the gullet
- pain in neck, back, extremities
- nail infection
- neoplasm (tumour) progression
- new cancers of the bone marrow or blood, such as acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS)
- liver damage
- bone marrow failure
- increased eosinophils in blood.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pixuvri

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).
Keep the vial in the outer carton in order to protect from light.

Pixuvri does not contain anything to prevent the growth of bacteria and it is, therefore, recommended that it be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C.

Reconstituted pixantrone solution is stable for up to 24 hours at room temperature (15°C to 25°C) in standard infusion bags.

Pixuvri is for single use only. Any unused medicinal product or waste material, including materials used for reconstitution, dilution, and administration should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Pixuvri contains
The active substance is pixantrone. Each vial contains 50 mg pixantrone dimaleate (equivalent to 29 mg pixantrone). The other ingredients are lactose monohydrate, sodium hydroxide, hydrochloric acid, and sodium chloride.

What Pixuvri looks like and contents of the pack
Pixuvri is a powder for concentrate for solution for infusion. It appears as a dark blue powder which comes in vials containing 29 mg of pixantrone. Pack size: 1 vial.

Marketing Authorisation Holder
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

Manufacturer
Les Laboratoires Servier Industrie
905 Route de Saran
45520 Gidy
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Detailed instructions for users

READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION

Special precautions for use
Pixuvri is an anticancer medicinal product that is harmful to cells; caution should be exercised in handling. Avoid contact with eyes and skin. Use gloves, masks, and protective eyewear when handling and during decontamination procedures. If Pixuvri (lyophilised powder or reconstituted liquid solution) contacts the skin, wash the skin immediately and flush the membranes thoroughly with water.

Reconstitution/preparation for intravenous administration
Each single-use vial of Pixuvri contains pixantrone dimaleate equivalent to 29 mg pixantrone. After reconstitution with 5 ml sodium chloride 9 mg/ml (0.9%) solution for injection, each ml of concentrate contains pixantrone dimaleate equivalent to 5.8 mg pixantrone.

Using sterile procedures, reconstitute each 29 mg vial with 5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. The powder should completely dissolve in 60 seconds with agitation. This yields a dark blue solution with a pixantrone concentration of 5.8 mg/ml.

Using sterile procedures, withdraw the volume needed for the required dose (based on 5.8 mg/ml concentration) and further dilute with sodium chloride 9 mg/ml (0.9%) solution for injection to a final volume of 250 ml.

Compatibility with other diluents has not been determined. After transferring, thoroughly mix the contents of the infusion bag. The mixture should be a dark blue solution.
Polyethersulfone 0.2 µm pore size in-line filters should be used during administration of the diluted Pixuvri solution.

In-use storage conditions
Pixuvri does not contain anything to prevent the growth of bacteria and it is therefore recommended that it be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C.

The reconstituted and diluted solution is stable for up to 24 hours at room temperature (15°C to 25°C) and daylight exposure in standard polyethylene (PE) infusion bags.

Special precautions for disposal and handling
Pixuvri is a cytotoxic agent. Any unused product or waste material should be disposed of in accordance with local requirements.

Devices and surfaces accidentally contaminated with Pixuvri must be treated with a solution of sodium hypochlorite (100 µl of water and 20 µl of sodium hypochlorite [7 ± 2% of available chlorine] for 0.58 mg of Pixuvri).

Equipment such as vials, needles and syringes used for Pixuvri administration should be handled as toxic waste.