ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Javlor 25 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of concentrate contains 25 mg of vinflunine (as ditartrate).

One 2 mL vial contains 50 mg of vinflunine (as ditartrate).
One 4 mL vial contains 100 mg of vinflunine (as ditartrate).
One 10 mL vial contains 250 mg of vinflunine (as ditartrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Javlor is indicated in monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

Efficacy and safety of vinflunine have not been studied in patients with performance status ≥ 2.

4.2 Posology and method of administration

Vinflunine treatment should be initiated under the responsibility of a physician qualified in the use of anticancer chemotherapy and is confined to units specialised in the administration of cytotoxic chemotherapy.

Before each cycle, adequate monitoring of complete blood counts should be conducted to verify the absolute neutrophil count (ANC), platelets and haemoglobin as neutropenia, thrombocytopenia and anaemia are frequent adverse reactions of vinflunine.

Posology
The recommended dose is 320 mg/m² vinflunine as a 20-minute intravenous infusion every 3 weeks.

In case of WHO/ECOG performance status (PS) of 1 or PS of 0 and prior pelvic irradiation, the treatment should be started at the dose of 280 mg/m². In the absence of any haematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² every 3 weeks for the subsequent cycles.

Recommended co-medication
In order to prevent constipation, laxatives and dietary measures including oral hydration are recommended from day 1 to day 5 or 7 after each vinflunine administration (see section 4.4).

Dose delay or discontinuation due to toxicity

Table 1: Dose delay for subsequent cycles due to toxicity

Toxicity	Day 1 treatment administration
Neutropenia (ANC < 1 000/mm^3) or Thrombocytopenia (platelets < 100 000/mm^3)	- Delay until recovery (ANC ≥ 1 000/mm^3 and platelets ≥ 100 000/mm^3) and adjust the dose if necessary (see table 2) - Discontinuation if recovery has not occurred within 2 weeks
Organ toxicity: moderate, severe or life threatening	- Delay until recovery to mild toxicity or none, or to initial baseline status and adjust the dose if necessary (see table 2) - Discontinuation if recovery has not occurred within 2 weeks
Cardiac ischaemia in patients with prior history of myocardial infarction or angina pectoris	- Discontinuation

Dose adjustments due to toxicity

Table 2: Dose adjustments due to toxicity

Toxicity	**Dose adjustment**				
(NCI CTC v 2.0)*	**Vinflunine initial dose of 320 mg/m²**			**Vinflunine initial dose of 280 mg/m²**	
	First Event	2nd consecutive event	3rd consecutive event	First Event	2nd consecutive event
Neutropenia Grade 4 (ANC < 500/mm^3) > 7 days	280 mg/m²	250 mg/m²	Definitive Treatment discontinuation	250 mg/m²	Definitive Treatment discontinuation
Febrile Neutropenia (ANC < 1 000/mm^3 and fever ≥ 38.5 °C)					
Mucositis or Constipation Grade 2 ≥ 5 days or Grade ≥ 3 any duration[1]					
Any other toxicity Grade ≥ 3 (severe or life-threatening) (except Grade 3 vomiting or nausea[2])					

*National Cancer Institute, Common Toxicity Criteria Version 2.0 (NCI CTC v 2.0)

[1] NCI CTC Grade 2 constipation is defined as requiring laxatives, Grade 3 as an obstipation requiring manual evacuation or enema, Grade 4 as an obstruction or toxic megacolon. Mucositis Grade 2 is defined as "moderate", Grade 3 as "severe" and Grade 4 as "life-threatening".

[2] NCI CTC Grade 3 nausea is defined as no significant intake, requiring intravenous fluids. Grade 3 vomiting as ≥ 6 episodes in 24 hours over pretreatment; or need for intravenous fluids.

Special populations

Patients with hepatic impairment

A pharmacokinetic and tolerability phase I study in patients with altered liver functions test has been completed (see section 5.2). Vinflunine pharmacokinetics was not modified in those patients, however based on hepatic biologic parameter modifications following vinflunine administration (gamma glutamyl transferases (GGT), transaminases, bilirubin), the dose recommendations are as follows:

- No dose adjustment is necessary in patients:
  - with a prothrombin time > 70% NV (Normal Value) and presenting at least one of the following criteria: **[** ULN (Upper Limit of Normal) < bilirubin ≤ 1.5×ULN and/or 1.5xULN < transaminases ≤ 2.5×ULN and/or ULN < GGT ≤ 5×ULN **]**.
  - with transaminases ≤ 2.5xULN (< 5xULN only in case of liver metastases).

- The recommended dose of vinflunine is 250 mg/m² given once every 3 weeks in patients with mild liver impairment (Child-Pugh grade A) or in patients with a prothrombin time ≥ 60% NV and 1.5×ULN < bilirubin ≤ 3×ULN and presenting at least one of the following criteria:
[transaminases > ULN and/or GGT > 5×ULN **]**.

- The recommended dose of vinflunine is 200 mg/m² given once every 3 weeks in patients with moderate liver impairment (Child-Pugh grade B) or in patients with a prothrombin time ≥ 50% NV and bilirubin > 3×ULN and transaminases > ULN and GGT > ULN.

Vinflunine has not been evaluated in patients with severe hepatic impairment (Child-Pugh grade C), or in patients with a prothrombin time < 50% NV or with bilirubin > 5xULN or with isolated transaminases > 2.5xULN (≥ 5xULN only in case of liver metastases) or with GGT > 15xULN.

Patients with renal impairment
In clinical studies, patients with CrCl (creatinine clearance) > 60 mL/min were included and treated at the recommended dose.
In patients with moderate renal impairment (40 mL/min ≤ CrCl≤ 60 mL/min), the recommended dose is 280 mg/m² given once every 3 weeks.
In patients with severe renal impairment (20 mL/min ≤ CrCl < 40 mL/min) the recommended dose is 250 mg/m² every 3 weeks (see section 5.2).

For further cycles, the dose should be adjusted in the event of toxicities, as shown in table 3 below.

Elderly patients (≥ 75 years)
No age-related dose modification is required in patients less than 75 years old (see section 5.2).
The doses recommended in patients of at least 75 years old are as follows:
- in patients of at least 75 years old but less than 80 years, the dose of vinflunine to be given is 280 mg/m² every 3 weeks.
- in patients 80 years old and above, the dose of vinflunine to be given is 250 mg/m² every 3 weeks.

For further cycles, the dose should be adjusted in the event of toxicities, as shown in table 3 below:

Table 3: Dose adjustments due to toxicity in renal impaired or elderly patients

<table>
<tr><td rowspan="2">Toxicity
(NCI CTC v 2.0)*</td><td colspan="4">Dose adjustment</td></tr>
<tr><td colspan="2">Vinflunine initial dose of 280 mg/m²</td><td colspan="2">Vinflunine initial dose of 250 mg/m²</td></tr>
<tr><td></td><td>First Event</td><td>2nd consecutive event</td><td>First Event</td><td>2nd consecutive event</td></tr>
<tr><td>Neutropenia Grade 4 (ANC < 500/mm³) > 7 days</td><td rowspan="4">250 mg/m²</td><td rowspan="4">Definitive Treatment discontinuation</td><td rowspan="4">225 mg/m²</td><td rowspan="4">Definitive Treatment discontinuation</td></tr>
<tr><td>Febrile Neutropenia (ANC < 1 000/mm³ and fever ≥ 38.5 °C)</td></tr>
<tr><td>Mucositis or Constipation Grade 2 ≥ 5 days or Grade ≥ 3 any duration[1]</td></tr>
<tr><td>Any other toxicity Grade ≥ 3 (severe or life-threatening) (except Grade 3 vomiting or nausea[2])</td></tr>
</table>

*National Cancer Institute, Common Toxicity Criteria Version 2.0 (NCI CTC v 2.0)
[1] NCI CTC Grade 2 constipation is defined as requiring laxatives, Grade 3 as an obstipation requiring manual evacuation or enema, Grade 4 as an obstruction or toxic megacolon. Mucositis Grade 2 is defined as "moderate", Grade 3 as "severe" and Grade 4 as "life-threatening".
[2] NCI CTC Grade 3 nausea is defined as no significant intake, requiring intravenous fluids. Grade 3 vomiting as ≥ 6 episodes in 24 hours over pretreatment; or need for intravenous fluids.

Paediatric population
There is no relevant use of Javlor in the paediatric population.

Method of administration
Precautions to be taken before handling or administering the medicinal product
Javlor must be diluted prior to administration. Javlor is for single use only.
For instructions on dilution of the medicinal product before administration, see section 6.6.

Javlor MUST ONLY be administered intravenously.
Javlor should be administered by a 20-minute intravenous infusion and NOT be given by rapid intravenous bolus.

Either peripheral lines or a central catheter can be used for vinflunine administration. When infused through a peripheral vein, vinflunine can induce venous irritation (see section 4.4). In case of small or sclerosed veins, lymphoedema or recent venipuncture of the same vein, the use of a central catheter may be preferred. To avoid extravasations it is important to be sure that the needle is correctly introduced before starting the infusion.

In order to flush the vein, administration of diluted Javlor should always be followed by at least an equal volume of sodium chloride 9 mg/mL (0.9%) solution for infusion or of glucose 50 mg/mL (5%) solution for infusion.
For detailed instructions on administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or other vinca alkaloids.
Recent (within 2 weeks) or current severe infection.
Baseline ANC < 1 500/mm^3 for the first administration, baseline ANC < 1 000/mm^3 for subsequent administrations (see section 4.4).
Platelets < 100 000/mm^3(see section 4.4).
Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Hematological toxicity
Neutropenia, leucopenia, anaemia and thrombocytopenia are frequent adverse reactions of vinflunine. Adequate monitoring of complete blood counts should be conducted to verify the ANC, platelet and haemoglobin values before each vinflunine infusion (see section 4.3).
Initiation of vinflunine is contraindicated in subjects with baseline ANC < 1 500/mm^3 or platelets < 100 000/mm^3. For subsequent administrations, vinflunine is contraindicated in subjects with baseline ANC < 1 000/mm^3 or platelets < 100 000/mm^3.
The recommended dose should be reduced in patients with haematological toxicity (see section 4.2).

Gastrointestinal disorders
Grade ≥ 3 constipation occurred in 15.3% of treated patients. NCI CTC Grade 3 constipation is defined as an obstipation requiring manual evacuation or enema, Grade 4 constipation as an obstruction or toxic megacolon. Constipation is reversible and can be prevented by special dietary measures such as oral hydration and fibre intake, and by administration of laxatives such as stimulant

laxatives or faecal softners from day 1 to day 5 or 7 of the treatment cycle. Patients at high risk of constipation (concomitant treatment with opiates, peritoneal carcinomas, abdominal masses, prior major abdominal surgery) should be medicated with an osmotic laxative from day 1 to day 7 administered once a day in the morning before breakfast.
In case of Grade 2 constipation, defined as requiring laxatives, for 5 days or more or Grade ≥ 3 of any duration, the dose of vinflunine should be adjusted (see section 4.2).

In case of any Grade ≥ 3 gastrointestinal toxicity (except vomiting or nausea) or of mucositis (Grade 2 for 5 days or more or Grade ≥ 3 of any duration) dose adjustment is required. Grade 2 is defined as "moderate", Grade 3 as "severe" and Grade 4 as "life-threatening" (see Table 2 in section 4.2).

Cardiac disorders
Few QT interval prolongations have been observed after the administration of vinflunine. This effect may lead to an increased risk of ventricular arrhythmias although no ventricular arrhythmias were observed with vinflunine. Nevertheless, vinflunine should be used with caution in patients with increase of the proarrhythmic risk (e.g. congestive heart failure, known history of QT interval prolongation, hypokalaemia) (see section 4.8). The concomitant use of two or more QT/QTc interval prolonging substances is not recommended (see section 4.5).
Special attention is recommended when vinflunine is administered to patients with prior history of myocardial infarction/ischaemia or angina pectoris (see section 4.8). Ischaemic cardiac events may occur, especially in patients who have underlying cardiac disease. Thus, patients receiving Javlor should be vigilantly monitored by physicians for the occurrence of cardiac events. Caution should be exercised in patients with a history of cardiac disease and the benefit / risk assessment should be carefully evaluated regularly. Discontinuation of vinflunine should be considered in patients who develop cardiac ischaemia.

Posterior Reversible Encephalopathy Syndrome (PRES)
Cases of PRES have been observed after administration of vinflunine.
The typical clinical symptoms are, with various degrees: neurological (headache, confusion, seizure, visual disorders), systemic (hypertension), and gastrointestinal (nausea, vomiting).
Radiological signs are white matter abnormalities in the posterior regions of the brain. Blood pressure should be controlled in patients developing symptoms of PRES. To confirm the diagnosis, brain imaging is recommended.
Clinical and radiological features usually resolved rapidly without sequelae after treatment discontinuation.
Discontinuation of vinflunine should be considered in patients who develop neurological signs of PRES (see section 4.8).

Hyponatraemia
Severe hyponatraemia, including cases due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), has been observed with the use of vinflunine (see section 4.8). Therefore, regular monitoring of serum sodium levels is recommended during treatment with vinflunine.

Hepatic impairment
The recommended dose should be reduced in patients with hepatic impairment (see section 4.2).

Renal impairment
The recommended dose should be reduced in patients with moderate or severe renal impairment (see section 4.2).

Elderly patients (≥ 75 years)
The recommended dose should be reduced in patients 75 years old and beyond (see section 4.2).

Interactions
The concomitant use of potent inhibitors or potent inducers of CYP3A4 with vinflunine should be avoided (see section 4.5).

Administration
Intrathecal administration of Javlor may be fatal.
When infused through a peripheral vein, vinflunine can induce Grade 1 (22% of the patients, 14.1% of the cycles), Grade 2 (11.0% of the patients, 6.8% of the cycles) or Grade 3 (0.8% of the patients, 0.2% of the cycles) venous irritation. All cases resolved rapidly without treatment discontinuation.
Instructions for administration should be followed as described in section 6.6.

Contraception
Men and women with reproductive potential must use an effective method of contraception during the treatment and respectively up to 4 and 7 months after the last vinflunine administration (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies showed that vinflunine had neither inducing effects on CYP1A2, CYP2B6 or CYP3A4 activity nor inhibition effects on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.

In vitro studies showed that vinflunine is a Pgp-substrate like other vinca alkaloids, but with a lower affinity. Therefore, risks of clinically significant interactions should be unlikely.
No pharmacokinetic interaction was observed in patients when vinflunine was combined with either cisplatin, carboplatin, capecitabine or gemcitabine.
No pharmacokinetic interaction was observed in patients when vinflunine was combined with doxorubicin. However, this combination was associated with a particularly high risk of haematological toxicity.

A phase I study evaluating the effect of ketoconazole treatment (a potent CYP3A4 inhibitor) on vinflunine pharmacokinetics indicated that co-administration of ketoconazole (400 mg orally once daily for 8 days) resulted in a 30% and 50% increase in blood exposures to vinflunine and its metabolite 4Odeacetyl-vinflunine (DVFL), respectively.

Therefore the concomitant use of vinflunine and potent CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole and grapefruit juice) or inducers (such as rifampicin and Hypericum perforatum (St John's wort)) should be avoided since they may increase or decrease vinflunine and DVFL concentrations (see section 4.4 and 5.2).

The concomitant use of vinflunine with others QT/QTc interval prolonging medicinal products should be avoided (see section 4.4).

A pharmacokinetic interaction between vinflunine and pegylated/liposomal doxorubicin was observed, resulting in a 15% to 30% apparent increase in vinflunine exposure and a 2 to 3-fold apparent decrease of doxorubicin AUC, whereas for doxorubicinol, the concentrations of the metabolite were not affected. According to an *in vitro* study, such changes could be related to adsorption of vinflunine on the liposomes and a modified blood distribution of both compounds. Therefore, caution should be excercised when this type of combination is used.

A possible interaction with paclitaxel and docetaxel (CYP3 substrates) has been suggested from an *in vitro* study (slight inhibition of vinflunine metabolism). No specific clinical studies of vinflunine in combination with these compounds have been carried out yet.

The concomitant use of opioids could enhance the risk of constipation.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Due to the genotoxic potential of vinflunine (see section 5.3), both male and female patients should take adequate and effective contraceptive measures during treatment and up to 4 months after the discontinuation of the therapy for men and 7 months after the discontinuation of therapy for women.

Pregnancy
There are no data available on the use of vinflunine in pregnant women. Studies in animals have shown embryotoxicity and teratogenicity (see section 5.3). On the basis of the results of animal studies and the pharmacological action of the medicinal product, there is a potential risk of embryonic and foetal abnormalities.
Vinflunine should therefore not be used during pregnancy, unless it is strictly necessary. If pregnancy occurs during treatment, the patient should be informed about the risk for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered. Genetic counselling is also recommended for patients wishing to have children after therapy.

Women of child-bearing potential
Women of child-bearing potential must use effective contraception during treatment and for 7 months after treatment.

Breast-feeding
It is unknown whether vinflunine or its metabolites are excreted in human milk. Due to the possible very harmful effects on the infants, breast-feeding during treatment with vinflunine is contraindicated (see section 4.3).

Fertility
Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinflunine.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, the following adverse effects have been reported with Javlor: fatigue, dizziness, vertigo, visual disturbance and syncope (see section 4.8). Patients should be advised not to drive or use machines without the advice of a healthcare professional.

4.8 Undesirable effects

Summary of the safety profile
The most frequent treatment-related adverse reactions reported in the two phase II and one phase III trials in patients with transitional cell carcinoma of the urothelium (450 patients treated with vinflunine) were haematological disorders, mainly neutropenia and anaemia; gastrointestinal disorders, especially constipation, anorexia, nausea, stomatitis/mucositis, vomiting, abdominal pain and diarrhoea, and general disorders such as asthenia/fatigue.

Tabulated list of adverse reactions
Adverse reactions are listed below by System Organ Class, frequency and grade of severity (NCI CTC version 2.0). Frequency of adverse reactions is defined using the following convention: 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 the available data**).** Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4 Adverse reactions observed in patients with transitional cell carcinoma of the urothelium treated with vinflunine

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3-4
Infections and infestations	Common	Neutropenic infection	2.4	2.4
		Infections (viral, bacterial, fungal)	7.6	3.6
	Uncommon	Neutropenic sepsis	0.2	0.2
Neoplasm benign, malignant and unspecified	Uncommon	Tumour pain	0.2	0.2
Blood and lymphatic system disorders	Very common	Neutropenia	79.6	54.6
		Leucopenia	84.5	45.2
		Anaemia	92.8	17.3
		Thrombocytopenia	53.5	4.9
	Common	Febrile neutropenia	6.7	6.7
Immune system disorders	Common	Hypersensitivity	1.3	0.2
Endocrine disorders	Uncommon	Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) [a]	0.4 [b]	0.4 [b]
Metabolism and nutrition disorders	Very common	Hyponatraemia	39.8	11.7
		Decreased appetite	34.2	2.7
	Common	Dehydration	4.4	2.0
Psychiatric disorders	Common	Insomnia	5.1	0.2
Nervous system disorders	Very common	Peripheral sensory neuropathy	11.3	0.9
	Common	Syncope	1.1	1.1
		Headache	6.2	0.7
		Dizziness	5.3	0.4
		Neuralgia	4.4	0.4
		Dysgeusia	3.3	0
		Neuropathy	1.3	0
	Uncommon	Peripheral motor neuropathy	0.4	0
	Rare	Posterior Reversible Encephalopathy Syndrome[a]	0.03[b]	0.03[b]
Eye disorders	Uncommon	Visual disturbance	0.4	0
Ear and Labyrinth disorders	Common	Ear pain	1.1	0
	Uncommon	Vertigo	0.9	0.4
		Tinnitus	0.9	0
Cardiac disorders	Common	Tachycardia	1.8	0.2
	Uncommon	Myocardial ischaemia	0.7	0.7
		Myocardial infarction	0.2	0.2
Vascular disorders	Common	Hypertension	3.1	1.6
		Venous thrombosis[c]	3.6	0.4
		Phlebitis	2.4	0
		Hypotension	1.1	0.2
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea	4.2	0.4
		Cough	2.2	0
	Uncommon	Acute respiratory distress syndrome	0.2	0.2
		Pharyngolaryngeal pain	0.9	0
Gastrointestinal disorders	Very common	Constipation	54.9	15.1
		Abdominal pain	21.6	4.7

		Vomiting	27.3	2.9
		Nausea	40.9	2.9
		Stomatitis	27.1	2.7
		Diarrhoea	12.9	0.9
	Common	Ileus	2.7	2.2
		Dysphagia	2.0	0.4
		Buccal disorders	4.0	0.2
		Dyspepsia	5.1	0.2
	Uncommon	Odynophagia	0.4	0.2
		Gastric disorders	0.8	0
		Oesophagitis	0.4	0.2
		Gingival disorders	0.7	0
Skin and subcutaneous tissue disorders	Very common	Alopecia	28.9	NA
	Common	Rash	1.8	0
		Urticaria	1.1	0
		Pruritus	1.1	0
		Hyperhidrosis	1.1	0
	Uncommon	Dry skin	0.9	0
		Erythema	0.4	0
Musculoskeletal and connective tissue disorders	Very common	Myalgia	16.7	3.1
	Common	Muscular weakness	1.8	0.7
		Arthralgia	7.1	0.4
		Back pain	4.9	0.4
		Pain in jaw	5.6	0
		Pain in extremity	2.4	0
		Bone pain	2.9	0
		Musculoskeletal pain	2.7	0.2
Renal and urinary disorders	Uncommon	Renal failure	0.2	0.2
General disorders and administration site conditions	Very common	Asthenia/Fatigue	55.3	15.8
		Injection site reaction	26.4	0.4
		Pyrexia	11.7	0.4
	Common	Chest pain	4.7	0.9
		Chills	2.2	0.2
		Pain	3.1	0.2
		Oedema	1.1	0
	Uncommon	Extravasation	0.7	0
Investigations	Very common	Weight decreased	24.0	0.4
	Uncommon	Transaminases increased	0.4	0
		Weight increased	0.2	0

[a]adverse reactions reported from post-marketing experience
[b]frequency calculated on the basis of non-TCCU clinical trial
[c]include: phlebitis (2.4%), deep vein thrombosis (0.4%), superficial phlebitis (0.2%), thrombophlebitis (0.2%) and superficial thrombophlebitis (0.2%)

Adverse reactions in all indications
Adverse reactions occurring in patients with transitional cell carcinoma of the urothelium and in patients with other disease than this indication and potentially severe or adverse reactions that are a class effect of the vinca alkaloids are described below:

Blood and lymphatic system disorders
Grade 3/4 neutropenia was observed in 43.8% of patients. Severe anaemia and thrombocytopenia were less common (respectively 8.8 and 3.1%). Febrile neutropenia defined as ANC < 1 000/mm^3 and fever ≥ 38.5 °C of unknown origin without clinically microbiologically documented infection (NCI

CTC version 2.0) was observed in 5.2% of patients. Infection with Grade 3/4 neutropenia was observed in 2.8% of patients.
Overall 8 patients (0.6% of the treated population) died from infection as a complication occurring during neutropenia.

Gastrointestinal disorders
Constipation is a class effect of the vinca alkaloids: 11.8% of patients experienced severe constipation during treatment with vinflunine. Grade 3/4 ileus reported in 1.9% of patients was reversible when managed by medical care. Constipation is managed by medical care (see section 4.4).

Nervous system disorders
Sensory peripheral neuropathy is a class effect of the vinca alkaloids. Grade 3 was experienced by 0.6% patients. All resolved during the study.
Rare cases of Posterior Reversible Encephalopathy Syndrome have been reported (see section 4.4).

Cardiovascular disorders
Cardiac effects are a known class effect of the vinca alkaloids. Myocardial infarction or ischaemia were experienced by 0.5% of the patients and most of them had a pre-existing cardiovascular disease or risk factors. One patient died after myocardial infarction and another one due to a cardiopulmonary arrest.
Few QT interval prolongations have been observed after the administration of vinflunine.

Respiratory, thoracic and mediastinal disorders
Dyspnoea occurred in 3.2% of the patients but was rarely severe (Grade 3/4: 1.2%).
Bronchospam was reported in one patient treated with vinflunine for a different setting from the indication.

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 reporting system listed in Appendix V.

4.9 Overdose

The main toxic effect due to an overdose with vinflunine is bone marrow suppression with a risk of severe infection.
There is no known antidote for vinflunine overdose. In case of overdose, the patient should be kept in a specialised unit and vital functions should be closely monitored. Other appropriate measures should be taken, such as blood transfusions, administration of antibiotics and growth factors.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, vinca alkaloids and analogues, ATC code: L01CA05

Mechanism of action
Vinflunine binds to tubulin at or near to the vinca binding sites inhibiting its polymerisation into microtubules, which results in treadmilling suppression, disruption of microtubule dynamic, mitotic arrest and apoptosis. *In vivo,* vinflunine displays significant antitumor activity against a broad spectrum of human xenografts in mice both in terms of survival prolongation and tumour growth inhibition.

Clinical efficacy and safety
One phase III and two phase II trials support the use of Javlor for treatment of advanced or metastatic transitional cell carcinoma of the urothelium as second-line therapy after failure of a prior platinum-containing regimen.

In the two multi-centre open-label, single-arm phase II clinical trials a total of 202 patients were treated with vinflunine.

In the multi-centre, open-label controlled phase III clinical trial, 253 patients were randomised to treatment with vinflunine + BSC (best supportive care) and 117 patients to the BSC arm.
The median overall survival was 6.9 months (vinflunine + BSC) vs. 4.6 months (BSC), but the difference did not reach statistical significance; hazard ratio 0.88 (95% CI 0.69, 1.12). However a statistically significant effect was seen on progression-free survival. Median PFS was 3.0 months (vinflunine + BSC) vs 1.5 months (BSC) (p=0.0012).

In addition a pre-specified multivariate analysis performed on the ITT population demonstrated that vinflunine had a statistically significant treatment effect (p=0.036) on overall survival when prognostic factors (PS, visceral involvement, alkaline phosphatases, haemoglobin, pelvic irradiation) were taken into consideration; hazard ratio 0.77 (95% CI 0.61, 0.98). A statistically significant difference on overall survival (p=0.040) was also seen in the eligible population (which excluded 13 patients with clinically significant protocol violations at baseline who were not eligible for treatment); hazard ratio 0.78 (95% CI 0.61, 0.99). This is considered the most relevant population for the efficacy analysis, as it most closely reflects the population intended for treatment.

Efficacy was demonstrated in both patients with or without prior cisplatin use.
In the eligible population, the subgroup analyses according to the prior cisplatin use versus BSC on overall survival (OS) showed a HR (95% CI) = [0.64 (0.40 – 1.03); p=0.0821] in the absence of prior cisplatin, and a HR (95% CI) = [0.80 (0.60 – 1.06); p=0.1263] in the presence of prior cisplatin. When adjusted on prognostic factors, the analyses of OS in the subgroups of patients without or with prior cisplatin showed a HR (95% CI) = [0.53 (0.32 – 0.88); p=0.0143] and a HR (95% CI) = [0.70 (0.53 – 0.94); p=0.0174], respectively.
In the subgroup analyses of prior cisplatin use versus BSC for progression free survival (PFS), the results were: HR (95% CI) = [0.55 (0.34 – 0.89); p=0.0129] in the absence of prior cisplatin, and a HR (95% CI) = [0.64 (0.48 – 0.85); p=0.0040] in the presence of prior cisplatin. When adjusted on prognostic factors, the analyses of PFS in the subgroups of patients without or with prior cisplatin showed a HR (95% CI) = [0.51(0.31 – 0.86); p=0.0111] and a HR (95% CI) = [0.63(0.48 – 0.84); p=0.0016], respectively.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Javlor in all subsets of the paediatric population in the treatment of ureter and bladder carcinoma and the treatment of breast carcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Vinflunine pharmacokinetics is linear in the range of administered doses (from 30 mg/m² to 400 mg/m^2) in cancer patients.
Blood exposure to vinflunine (AUC), significantly correlated with severity of leucopenia, neutropenia and fatigue.

Distribution
Vinflunine is moderately bound to human plasma proteins (67.2±1.1%) with a ratio between plasma and whole blood concentrations of 0.80±0.12. Protein binding mainly involves high density lipoproteins and serum albumin and is non-saturable on the range of vinflunine concentrations observed in patients. Binding to alpha-1 acid glycoprotein and to platelets is negligible (< 5%).

The terminal volume of distribution is large, 2422±676 litres (about 35 l/kg) suggesting extensive distribution into tissues.

Biotransformation
All metabolites identified are formed by the cytochrome CYP3A4 isoenzyme, except for 4-O-deacetylvinflunine (DVFL), the only active metabolite and main metabolite in blood which is formed by multiple esterases.

Elimination
Vinflunine is eliminated following a multi-exponential concentration decay, with a terminal half-life ($t_{1/2}$) close to 40 h. DVFL is slowly formed and more slowly eliminated than vinflunine ($t_{1/2}$ of approximately 120 h).
The excretion of vinflunine and its metabolites occurs through faeces (2/3) and urine (1/3).
In a population pharmacokinetic analysis in 372 patients (656 pharmacokinetic profiles), the total blood clearance was 40 L/h with low inter and intra-individual variability (25% and 8%, respectively, expressed as coefficient of variation).

Pharmacokinetics in special populations

Hepatic impairment
No modification of vinflunine and DVFL pharmacokinetics was observed in 25 patients presenting varying degrees of hepatic impairment, compared to patients with normal hepatic function. This was further confirmed by the population pharmacokinetic analysis (absence of relationship between vinflunine clearance and biology markers of hepatic impairment). However, dose adjustments are recommended in patients with liver impairment (see section 4.2).

Renal impairment
A pharmacokinetic phase I study was performed in 2 groups of patients with renal impairment classified according to the calculated creatinine clearance (CrCl) values: group 1 (n=13 patients) with moderate impairment (40 mL/min ≤ CrCl ≤ 60 mL/min) and group 2 (n=20 patients) with severe impairment (20 mL/min ≤ CrCl < 40 mL/min). The pharmacokinetic results of this study indicated a reduction of vinflunine clearance when CrCl is decreased. This is further confirmed by the population pharmacokinetic analysis (56 patients with CrCl between 20 mL/min and 60 mL/min), showing that vinflunine clearance is influenced by the creatinine clearance value (Cockcroft and Gault formula). Dose adjustments are recommended in patients with moderate and severe renal impairment (see section 4.2).

Elderly (≥ 75 years)
A pharmacokinetic phase I study of vinflunine was performed in elderly patients (n=46). Vinflunine doses were adjusted according to 3 age groups as shown below:

Age (y)	Number of patients	Vinflunine (mg/m²)
[70 – 75 [	17	320
[75 – 80 [	15	280
≥ 80	14	250

Vinflunine clearance was significantly decreased in patients ≥ 80 years old as compared to a control group of younger patients < 70 years.
Pharmacokinetics of vinflunine was not modified for patients 70 ≤ age < 75 years and 75 ≤ age < 80 years.
Based on both PK and safety data, dose reductions are recommended in the elder groups: 75 ≤ age < 80 years; and age ≥ 80 years.
For further cycles the dose should be adjusted in the event of toxicities (see section 4.2).

Others
According to the population pharmacokinetic analysis, neither gender nor performance status (ECOG score) had an impact on vinflunine clearance which is directly proportional to body surface area.

5.3 Preclinical safety data

Imaging distribution studies following radioactive vinflunine in rats, illustrated that the compound levels in lungs, kidneys, liver, salivary and endocrine glands, and gastrointestinal tract were rapidly higher than those in blood.

Preclinical data revealed moderate to severe neutropenia and mild anaemia, in all species tested, with liver toxicity in dogs and rats (characterized by dose-dependent increases in liver transaminases and hepatic necrosis/hepatocellular alterations at high doses). These toxic effects were dose-related and fully or partially reversible following a 1-month recovery period. Vinflunine did not induce peripheral neuropathy in animals.
Vinflunine has shown to be clastogenic (induces chromosome breakage) in the *in vivo* micronucleus test in rat as well as mutagenic and clastogenic in a mouse lymphoma assay (without metabolic activation).

The carcinogenic potential of vinflunine has not been studied.
In the reproduction studies, vinflunine appeared to be embryolethal and teratogenic in rabbits and teratogenic in rats. During the pre- and post-natal development study in rat, vinflunine induced malformations of the uterus and vagina in 2 females, and adversely affected mating and/or ovule implantation and markedly lowered the number of *concepti.*

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

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
3 years.

Diluted solution
Chemical and physical in-use stability has been demonstrated for the diluted medicinal product as follows:

- protected from light in polyethylene or polyvinylchloride infusion bag: for up to 6 days in a refrigerator (2 °C-8 °C) or for up to 24 hours at 25 °C;
- exposed to light in polyethylene or polyvinylchloride infusion set for up to 1 hour at 25 °C.

From a microbiological point of view, the product should be used immediately after dilution. 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 dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).
Store in the original package in order to protect from light.

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

6.5 Nature and contents of container

Colourless type I glass vials closed by a grey laminated butyl rubber stopper or black chlorobutyl stopper covered with an aluminium flip-off seal with yellow bonnet for 2 mL vial (50 mg vinflunine) or pink bonnet for 4 mL vial (100 mg vinflunine) or orange bonnet for 10 mL vial (250 mg vinflunine) of concentrate for solution for infusion.

Pack size of 1 and 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General precautions for preparation and administration.
Vinflunine is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised in handling Javlor. Procedure for proper handling and disposal of anticancer medicinal products should be considered. All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood. Javlor solution for infusion should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Javlor. The use of gloves, goggles and protective clothing is recommended.
If the solution comes into contact with the skin, this should be washed immediately and thoroughly with soap and water. If it comes into contact with mucous membranes, the membranes should be flushed thoroughly with water.

Dilution of the concentrate
The volume of Javlor (concentrate) corresponding to the calculated dose of vinflunine should be mixed in a 100 mL bag of sodium chloride 9 mg/mL (0.9%) solution for infusion. Glucose 50 mg/mL (5%) solution for infusion may also be used. The diluted solution should be protected from light until administration (see section 6.3).

Method of administration
Javlor is for intravenous use ONLY.
Javlor is for single use only.
After dilution of the Javlor concentrate, the solution for infusion will be administered as follows:

- A venous access should be established for a 500 mL bag of sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for infusion, on a large vein preferably in the upper part of the forearm or using a central venous line. The veins of the hand dorsum and those close to joints should be avoided.
- The intravenous infusion should be started with half of the 500 mL bag of sodium chloride 9 mg/mL (0.9%) solution for infusion or of glucose 50 mg/mL (5%) solution for infusion, i.e. 250 mL, at a free flowing rate to flush the vein.
- The Javlor solution for infusion should be piggy-backed to the side injection port closest to the 500 mL bag to further dilute Javlor during administration.
- The Javlor solution for infusion should be infused over 20 minutes.
- The patency should be assessed frequently and extravasation precautions should be maintained throughout the infusion.

- After the infusion is completed, the remaining 250 mL from the sodium chloride 9 mg/mL (0.9%) solution for infusion or of glucose 50 mg/mL (5%) solution for infusion bag should be run at a flowing rate of 300 mL/h. In order to flush the vein, administration of Javlor solution for infusion should always be followed by at least an equal volume of sodium chloride 9 mg/mL (0.9%) solution for infusion or of glucose 50 mg/mL (5%) solution for infusion.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic medicinal products.

7. MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/550/001-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 September 2009
Date of the latest renewal: 16 May 2014

10. DATE OF REVISION OF THE TEXT

XX month YYYY

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(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

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

FAREVA PAU
FAREVA PAU 1
Avenue du Béarn
64320 Idron
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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Javlor 25 mg/mL concentrate for solution for infusion
vinflunine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One mL of concentrate contains 25 mg of vinflunine (as ditartrate).

One 2 mL vial contains 50 mg of vinflunine (as ditartrate)
One 4 mL vial contains 100 mg of vinflunine (as ditartrate)
One 10 mL vial contains 250 mg of vinflunine (as ditartrate)

3. LIST OF EXCIPIENTS

Water for injections as excipient.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 vial of 2 mL
10 vials of 2 mL
1 vial of 4 mL
10 vials of 4 mL
1 vial of 10 mL
10 vials of 10 mL

50 mg /2 mL
100 mg /4 mL
250 mg /10 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use ONLY, after dilution.
Fatal if given by other routes.
Read the package leaflet before 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:
Read the leaflet for the shelf life of diluted medicine.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Store in the original package 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 medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/550/001 (box of 1 vial of 2 mL with grey stopper)
EU/1/09/550/002 (box of 10 vials of 2 mL with grey stopper)
EU/1/09/550/003 (box of 1 vial of 4 mL with grey stopper)
EU/1/09/550/004 (box of 10 vials of 4 mL with grey stopper)
EU/1/09/550/005 (box of 1 vial of 10 mL with grey stopper)
EU/1/09/550/006 (box of 10 vials of 10 mL with grey stopper)
EU/1/09/550/007 (box of 1 vial of 2 mL with black stopper)
EU/1/09/550/008 (box of 10 vials of 2 mL with black stopper)
EU/1/09/550/009 (box of 1 vial of 4 mL with black stopper)
EU/1/09/550/010 (box of 10 vials of 4 mL with black stopper)
EU/1/09/550/011 (box of 1 vial of 10 mL with black stopper)
EU/1/09/550/012 (box of 10 vials of 10 mL with black stopper)

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}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Javlor 25 mg/mL sterile concentrate
vinflunine
IV use ONLY, after dilution

2. METHOD OF ADMINISTRATION

See leaflet

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg/2 mL
100 mg/4 mL
250 mg/10 mL

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Javlor 25 mg/mL concentrate for solution for infusion
vinflunine

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 effects, 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 Javlor is and what it is used for

Javlor contains the active substance vinflunine, which belongs to a group of anticancer medicines called vinca alkaloids. These medicines affect cancer cell growth by stopping cell division, leading to cell death (cytotoxicity).

Javlor is used to treat advanced or metastatic cancer of the bladder and urinary tract when a previous therapy with platinum-containing medicines has failed.

2. What you need to know before you use Javlor

Do not use Javlor
- if you are allergic to the active substance (vinflunine) or to other vinca alkaloids (vinblastine, vincristine, vindesine, vinorelbine),
- if you have had (in the last 2 weeks) or currently have a severe infection,
- if your levels of white blood cells and/or platelets are too low,
- if you are breast-feeding.

Warnings and precautions
Tell your doctor:
- if you have liver, kidney or heart problems,
- if you experience any neurological symptoms which could be a sign of "posterior reversible encephalopathy syndrome": brain swelling with usually temporary effects such as headaches, changed mental state which may lead to confusion and coma, convulsions, changes in vision, high blood pressure, nausea and vomiting as you may need to stop taking this medicine,
- if you experience symptoms of hyponatraemia (low blood sodium levels) or a "syndrome of inappropriate antidiuretic hormone secretion" such as headache, tiredness, seizures or coma. Regular monitoring of serum sodium levels is recommended during treatment with Javlor.
- if you are taking other medicines mentioned in "Other medicines and Javlor" below,
- if you have constipation, or if you are treated with medicines against pain (opioids), or if you have an abdominal cancer, or if you had a previous abdominal surgery. Constipation is a very common side effect of Javlor. To prevent constipation you may be given laxatives.

- if you would like to have a child (see important recommendations for men and women in "Pregnancy, breast-feeding and fertility" below).

Your blood cell counts will be checked regularly before and during your treatment, since low counts of blood cells is a very common side effect with Javlor.
Intrathecal administration of Javlor may be fatal. Javlor must not be given to you intrathecally (into the spine).

Children and adolescents
Javlor is not intended for use in children and adolescents.

Other medicines and Javlor
Tell your doctor if you are taking, have recently taken or might take any other medicines.

In particular, you should tell your doctor if you are taking medicines containing any of the following active substances:
- ketoconazole and itraconazole, used to treat fungal infection,
- opioids, used to treat pain,
- ritonavir, used to treat HIV infection,
- doxorubicin, pegylated liposomal doxorubicin, paclitaxel and docetaxel used to treat some kinds of cancer,
- rifampicin, used to treat tuberculosis or meningitis,
- herbal preparation containing hypericum perforatum (St John's wort) used to treat minor to moderate depression.

Or if you are taking medicines known to cause changes to the electrocardiogram (ECG), especially medicines known to cause "QT interval prolongation".

Javlor with food and drink
You should tell your doctor if you are drinking grapefruit juice since it may increase the effect of Javlor.
You should also drink water and eat high fibre foods.

Pregnancy, breast-feeding and fertility
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 starting your therapy.

If you are a woman or a man of reproductive potential, you must use an adequate and effective method of contraception during treatment and for 4 months if you are a man, or 7 months if you are a woman, after your last dose of Javlor.

Pregnancy
You should not be given Javlor if you are pregnant, unless it is absolutely necessary.
If you become pregnant during treatment, you should be informed about the risk for the unborn child and be monitored carefully.

Breast-feeding
You must not breastfeed during treatment with Javlor.

Fertility
If you would like to father a child, seek advice from your doctor. You may want to seek counseling on sperm storage before starting your therapy because of the possibility of irreversible infertility due to therapy with vinflunine.

Driving and using machines
Javlor may cause side effects such as tiredness, dizziness, vertigo, visual disturbance and fainting. Do not drive or use machines without advice from your doctor.

3. How to use Javlor

Dose
The recommended dose in adult patients is 320 mg/m² body surface (this is calculated by the doctor based on your weight and your height). The treatment will be repeated every 3 weeks.

Dose adjustment by age is not necessary for patients under 75 years of age. Your doctor will adjust your dose if your are 75 years old or over.

Your doctor will also adjust the starting dose of Javlor based on your physical conditions and in specific situations:
- if you had a previous irradiation of the pelvis
- if you have moderate or severe kidney problems
- if you have liver problems.

During treatment, your doctor may reduce the dose of Javlor, delay or interrupt the treatment if you experience certain side effects.

How Javlor is given
Javlor MUST ONLY be administered intravenously.
Javlor will be given to you by a healthcare professional (qualified in the use of cancer treatment in healthcare specialised units) as an intravenous infusion (drip into your vein) lasting 20 minutes.
Javlor is a concentrate that has to be diluted before administration.

If you are given more Javlor than you should receive
This medicine will be given by your doctor or nurse. In the event that you are given too much (an overdose), your doctor will check you for side effects.

If you forget to use Javlor
It is very important that you do not miss a dose of this medicine. If you miss an appointment, **call your doctor straight away** to reschedule your appointment.

If you stop using Javlor
Your doctor will decide when you should stop your treatment. If you wish to stop prematurely the treatment, you will need to discuss the other treatment options available to you with your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

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

Tell your doctor immediately if you develop any of the following serious side effects while being treated with Javlor:
- fever and / or chills which could be signs of infection,
- chest pain which could be sign of heart attack,
- constipation that resists to laxative treatment,
- neurological symptoms which could be a sign of “posterior reversible encephalopathy syndrome”: brain swelling with usually temporary effects such as headaches, changed mental state which may lead to confusion and coma, convulsions, changes in vision, high blood pressure, nausea and vomiting (see section 2 “warnings and precautions”).

Other side effects may include:
Very common (may affect more than 1 in 10 people)

- abdominal pain, nausea, vomiting
- constipation, diarrhoea
- inflammation of the mucosa of the mouth (stomatitis)
- tiredness (asthenia), muscle pain (myalgia)
- lack of sense of touch due to nerve damage (peripheral sensory neuropathy)
- weight decrease, decrease of appetite
- loss of hair (alopecia)
- reactions at injection site (pain, redness, swelling)
- fever
- low levels of white blood cells, red blood cells and/or platelets (seen in blood test)
- low levels of blood sodium (hyponatraemia) seen in blood test.

Common (may affect up to 1 in 10 people)
- infections (neutropenic infection, febrile neutropenia, infections (viral, bacterial, fungal)) with symptoms such as high fever and deterioration in general health
- chills, excessive sweating (hyperhidrosis), pain
- allergy (hypersensitivity), dehydration, headache, skin rash, itching (pruritus), urticaria
- loss of movement in bowel muscles (ileus), digestive problems (dyspepsia), difficulty swallowing (dysphagia), buccal disorders (pain in the mouth, on the tongue and toothache), taste alteration
- muscular weakness, pain in jaw, pain in extremity, back pain, pain in joints, muscular pain, bone pain, ear pain
- dizziness, insomnia, transiant loss of consciousness (fainting)
- difficulties with body movements due to nerve damage (neuropathy) and nerve pain (neuralgia)
- fast heartbeat (tachycardia), raised blood pressure, reduced blood pressure
- breathing difficulties (dyspnoea), cough, chest pain
- swelling of your arms, hands, feet, ankles, legs or other parts of your body (oedema)
- inflammation of the veins (phlebitis) and formation of blood clots in the blood vessels (vein thrombosis).

Uncommon (may affect up to 1 in 100 people)
- blood infection with low levels of white blood cells (neutropenic sepsis)
- visual disturbances
- dry skin, redness of the skin (erythema)
- nerve damage causing muscle contraction disorders (peripheral motor neuropathy)
- inflammation of the tube that leads to the stomach (oesophagitis), pain swallowing (odynophagia), pain in the throat (pharolaryngeal pain), gum disorders
- weight increase
- urinary problems that could be a sign of inability of the kidneys to work properly (renal failure)
- ringing or buzzing in the ears (tinnitus)
- increase in liver enzymes (transaminases) seen in blood test
- “Syndrome of inappropriate antidiuretic hormone secretion”, which is a condition that causes low levels of blood sodium
- tumour pain
- spinning sensation (vertigo)
- heart attack (myocardial infarction), reduced blood supply (myocardial ischaemia)
- difficulty breathing, which may be the symptom of a condition known as acute respiratory distress syndrome and can be severe and life-threatening
- extravasation (when a medicine that is normally injected into a vein leaks or is accidentally injected into the tissue surrounding the vein, where it can cause serious damage).

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 Javlor

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 the carton after EXP.

It is most unlikely that you will be asked to store this medicine yourself.
Storage conditions are detailed in the section intended for medicinal or heathcare professionals.

Unopened vials
Store in a refrigerator (2 °C-8 °C).
Store in the original package in order to protect from light.

Diluted solution
The diluted solution should be used immediately.

Do not throw away any medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other information

What Javlor contains
- The active substance is vinflunine. Each mL of concentrate contains 25 mg of vinflunine (as ditartrate).
  One 2 mL vial contains 50 mg of vinflunine (as ditartrate).
  One 4 mL vial contains 100 mg of vinflunine (as ditartrate).
  One 10 mL vial contains 250 mg of vinflunine (as ditartrate).
- The other ingredient is water for injections.

What Javlor looks like and contents of the pack

Javlor is a clear, colourless to pale yellow solution. It comes in colourless glass vials closed by a rubber stopper covered with an aluminium flip-off seal with yellow bonnet for 2 mL vial, pink bonnet for 4 mL vial or orange bonnet for 10 mL vial of concentrate.
Each pack contains 1 or 10 vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

Manufacturer

FAREVA PAU
FAREVA PAU 1
Avenue du Béarn
64320 Idron
France

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in MM/YYYY

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

<----------->
The following information is intended for medical or healthcare professionals only:

INSTRUCTION FOR USE

General precautions for preparation and administration.
Vinflunine is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised in handling Javlor. Procedure for proper handling and disposal of anticancer medicinal products should be considered. All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood. Javlor solution for infusion should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Javlor. The use of gloves, goggles and protective clothing is recommended.
If the solution comes into contact with the skin, this should be washed immediately and thoroughly with soap and water. If it comes into contact with mucous membranes, the membranes should be flushed thoroughly with water.

Dilution of the concentrate
The volume of Javlor (concentrate) corresponding to the calculated dose of vinflunine should be mixed in a 100 mL bag of sodium chloride 9 mg/mL (0.9%) solution for infusion. Glucose 50 mg/mL (5%) solution for infusion may also be used. The diluted solution should be protected from light until administration (see section 6.3).

Method of administration
Javlor is for intravenous use ONLY.
Javlor is for single use only.
After dilution of the Javlor concentrate, the solution for infusion will be administered as follows:

- A venous access should be established for a 500 mL bag of sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for infusion, on a large vein preferably in the upper part of the forearm or using a central venous line. The veins of the hand dorsum and those close to joints should be avoided.
- The intravenous infusion should be started with half of the 500 mL bag of sodium chloride 9 mg/mL (0.9%) solution for infusion or of glucose 50 mg/mL (5%) solution for infusion, i.e. 250 mL, at a free flowing rate to flush the vein.
- The Javlor solution for infusion should be piggy-backed to the side injection port closest to the 500 mL bag to further dilute Javlor during administration.
- The Javlor solution for infusion should be infused over 20 minutes.
- The patency should be assessed frequently and extravasation precautions should be maintained throughout the infusion.

- After the infusion is completed, the remaining 250 mL from the sodium chloride 9 mg/mL (0.9%) solution for infusion or of glucose 50 mg/mL (5%) solution for infusion bag should be run at a flowing rate of 300 mL/h. In order to flush the vein, administration of Javlor solution for infusion should always be followed by at least an equal volume of sodium chloride 9 mg/mL (0.9%) solution for infusion or of glucose 50 mg/mL (5%) solution for infusion.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic medicinal products.

Storage conditions
Unopened vials
Store in a refrigerator (2 °C-8 °C).
Store in the original packaging in order to protect from light.

Diluted solution
Chemical and physical in-use stability has been demonstrated for the diluted medicinal product as follows:

- protected from light in polyethylene or polyvinylchloride infusion bag: for up to 6 days in a refrigerator (2 °C-8 °C) or for up to 24 hours at 25 °C;
- exposed to light in polyethylene or polyvinylchloride infusion set: for up to 1 hour at 25 °C.

From a microbiological point of view, the product should be used immediately after dilution. 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 dilution has taken place in controlled and validated aseptic conditions.