

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 < 1000 /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 (NCI CTC v 2.0)*	Dose adjustment				
	Vinflunine initial dose of 320 mg/m ²			Vinflunine initial dose of 280 mg/m ²	
	First Event	2 nd consecutive event	3 rd consecutive event	First Event	2 nd consecutive event
Neutropenia Grade 4 (ANC < 500/mm ³) > 7 days	280 mg/m ²	250 mg/m ²	Definitive Treatment discontinuation	250 mg/m ²	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 obstruction 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 $\leq 1.5 \times$ ULN and/or $1.5 \times$ ULN $<$ Transaminases $\leq 2.5 \times$ ULN and/or ULN $<$ GGT $\leq 5 \times$ ULN].

- with transaminases $\leq 2.5 \times$ ULN ($< 5 \times$ ULN 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 $\geq 60\%$ NV and $1.5 \times$ ULN $<$ bilirubin $\leq 3 \times$ ULN and presenting at least one of the following criteria: [transaminases $>$ ULN and/or GGT $> 5 \times$ 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 $\geq 50\%$ NV and bilirubin $> 3 \times$ 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 $> 5 \times$ ULN or with isolated Transaminases $> 2.5 \times$ ULN ($\geq 5 \times$ ULN only in case of liver metastases) or with GGT $> 15 \times$ ULN.

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 \leq 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 \leq 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

Toxicity (NCI CTC v 2.0)*	Dose adjustment			
	Vinflunine initial dose of 280 mg/m ²		Vinflunine initial dose of 250 mg/m ²	
	First Event	2 nd consecutive event	First Event	2 nd consecutive event
Neutropenia Grade 4 (ANC $< 500/\text{mm}^3$) > 7 days	250 mg/m ²	Definitive Treatment discontinuation	225 mg/m ²	Definitive Treatment discontinuation
Febrile Neutropenia (ANC $< 1,000/\text{mm}^3$)				

and fever $\geq 38,5$ °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.

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 $< 1,500/\text{mm}^3$ for the first administration, baseline ANC $< 1,000/\text{mm}^3$ for subsequent administrations (see section 4.4).

Platelets $< 100,000/\text{mm}^3$ (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 $< 1,500/\text{mm}^3$ **or platelets $< 100,000/\text{mm}^3$. For subsequent administrations, vinflunine is contraindicated in subjects with baseline ANC $< 1,000/\text{mm}^3$ or platelets $< 100,000/\text{mm}^3$.**

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 softeners 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 up to 3 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 medical 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 exercised 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

Both male and female patients should take adequate contraceptive measures up to three months after the discontinuation of the therapy.

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.

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

Javlor may cause adverse reactions such as fatigue (very common) and dizziness (common) which may lead to a minor or moderate influence on the ability to drive and use machines. Patients should be advised not to drive or use machines if they experience any adverse reaction with a potential impact on the ability to perform these activities (see section 4.8).

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from 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	Tumor 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	
		Vein thrombosis	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	

	Common	Diarrhoea	12.9	0.9
		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
Skin and subcutaneous tissue disorders	Very common	Alopecia	28.9	NA
		Rash	1.8	0
	Common	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

^aadverse reactions reported from post-marketing experience

^bfrequency calculated on the basis of non-TCCU clinical trial

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/mm³ 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%).

Bronchospasm 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(<http://forms.gov.it/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.it>) or by email (adr@MOH.HEALTH.GOV.IT).

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/m²) 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 ($40 \text{ mL/min} \leq \text{CrCl} \leq 60 \text{ mL/min}$) and group 2 (n=20 patients) with severe impairment ($20 \text{ mL/min} \leq \text{CrCl} < 40 \text{ mL/min}$). 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/m ²)
[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 $70 \leq \text{age} < 75$ years and $75 \leq \text{age} < 80$ years.

Based on both PK and safety data, dose reductions are recommended in the elder groups: $75 \leq \text{age} < 80$ years; and $\text{age} \geq 80$ 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 embryo-lethal 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

Clear type I glass vials closed by a grey butyl or black chlorobutyl rubber stopper with aluminium flip-off seal with a bonnet. Each vial contains either 2 mL (50 mg vinflunine), 4 mL (100 mg vinflunine) or 10 mL (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. The use of gloves, goggles and protective clothing is recommended.

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. Javlor is for single use only.

If the solution comes into contact with the skin, the skin 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. MANUFACTURER

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8. REGISTRATION NUMBER

148-69-33536

9. LICENSE HOLDER

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10. DATE OF REVISION OF THE TEXT

September 2014