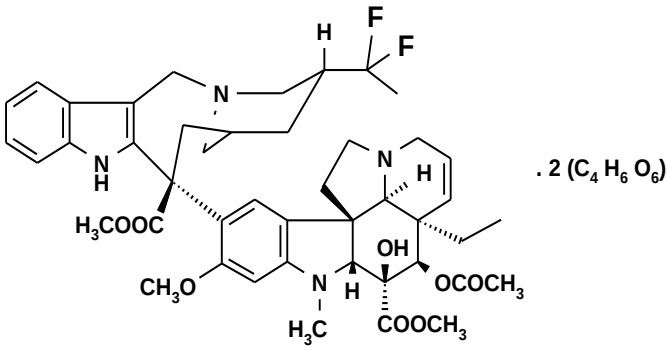
PRODUCT INFORMATION

JAVLOR®
25 mg/mL Concentrated Injection

NAME OF THE MEDICINE

vinflunine ditartrate



CAS number: 194468-36-5

DESCRIPTION

Vinflunine ditartrate is a white to off-white powder with the molecular formula $C_{53}H_{66}F_2N_4O_{20}$ and a molecular weight of 1117.09. Vinflunine ditartrate is freely soluble in water, soluble in ethanol and practically insoluble in dichloromethane. It is very hygroscopic with a pKa value of 5.67 and 8.17 in water at 26°C – 27°C.

Javlor Concentrated Injection is presented as a clear, colourless to pale yellow solution. It is supplied as a sterile, endotoxin-free aqueous solution intended for dilution with a suitable parenteral fluid (sodium chloride 0.9% solution or glucose 5% solution). One mL of Javlor contains 25 mg of vinflunine (as vinflunine ditartrate). Javlor also contains the excipient, water for injections.

PHARMACOLOGY

Pharmacodynamics

Vinflunine is an antineoplastic drug. 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 dynamics, mitotic arrest and apoptotic cell death.

In vivo, vinflunine displays significant antitumour activity against a broad spectrum of human xenografts in mice both in terms of survival prolongation and tumour growth inhibition.

Pharmacokinetics

Vinflunine pharmacokinetics is linear up 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 protein (67.2 ± 1.1%) with a plasma/blood concentration ratio of 0.80 ± 0.12. Protein binding mainly involves high density lipoproteins and serum albumin and is non-saturable in 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: 35 ± 9 L/kg suggesting extensive distribution into tissues.

Metabolism

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

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 (coefficients of variation of 25% and 8% respectively).

CLINICAL TRIALS

The efficacy of vinflunine as second line therapy for the treatment of patients with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) after failure of a prior platinum-containing regimen and with a Performance Status of ≤ 1

was demonstrated in one phase III (VFL 302) and two phase II (VFL 202 and CA 001) clinical trials.

The phase III clinical trial was an open-label, randomised, multi-centre study comparing vinflunine plus best supportive care to best supportive care (BSC) alone in patients with advanced TCCU previously treated with a first-line platinum-containing chemotherapy. Two hundred and fifty three patients were randomised to the vinflunine + BSC arm and 117 patients to the BSC arm. The vinflunine dose was 320 mg/m^2 for patients with performance status of 0 and without previous pelvic irradiation and 280 mg/m^2 escalated to 320 mg/m^2 for patients with performance status of 1 or previous pelvic irradiation. The dose was given by intravenous infusion over 20 minutes every 3 weeks.

Vinflunine did not significantly increase overall survival, the primary endpoint, in the intent-to-treat analysis. There was a small significant increase in progression-free survival of median 1.5 months (Table 1).

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 (performance status (PS), visceral involvement, alkaline phosphatases, haemoglobin, pelvic irradiation) were taken into consideration (Table 1). A statistically significant difference in overall survival with vinflunine treatment (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) (Table 1).

Table 1. Efficacy Results of the Phase III Trial (VFL 302) – Advanced or Metastatic Transitional Cell Carcinoma of the Urothelial Tract 2nd Line.

	VFL + BSC	**BSC**	**Difference/Hazard Ratio [95% CI]**
Evaluable Patients	n = 185	n = 85	
Overall Response Rate[1] (Complete + Partial) %	8.6 (0 + 8.6)	0 (0+0)	8.6 [5.0, 13.7]
Intent-to-Treat	n = 253	n = 117	
Progression-Free Survival[1] *median months*	3.0	1.5	p = 0.0012
Overall Survival *median months*	6.9	4.6	0.88 [0.69, 1.12]
Overall Survival (adjusted)[2]			0.77 [0.61, 0.98]

Eligible Patients	n = 249	n = 108	
Overall Survival *median months*	6.9	4.3	0.78 [0.61, 0.99]

VFL: Vinflunine; BSC: Best Supportive Care; [1] Independent Review; [2] Cox proportional hazards model.

In the two multi-centre, open-label, single-arm phase II clinical trials, a total of 202 patients were treated with vinflunine (VFL 202: n=51, CA 001: n=151). The median progression-free survival was 3.0 months and 2.7 months respectively. The median survival was 6.6 months and 7.9 months respectively.

INDICATIONS

Treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

CONTRAINDICATIONS

- Hypersensitivity to vinflunine or other vinca alkaloids.
- Recent (within 2 weeks) or current severe infection.
- Baseline absolute neutrophil count (ANC) < 1.5 x 10^9/L for the first administration, baseline ANC < 1.0 x 10^9/L for subsequent administrations**.
- Platelets < 100 x 10^9/L
- Lactation (see PRECAUTIONS – Use in lactation).

PRECAUTIONS

Performance Status

Vinflunine has a narrow safety threshold. If vinflunine is used in patients with poor performance status or patients likely to progress quickly to poor performance status, close observation is required since toxicity may be excessive.

For patients with WHO/ECOG performance status 1, vinflunine dose reduction is recommended (see DOSAGE AND ADMINISTRATION).

For patients with WHO/ECOG performance status 2 or greater, physicians should carefully consider the benefits and risks of vinflunine since there is no experience of the use of vinflunine in such patients.

Haematological toxicity
Neutropenia, leukopenia, anaemia and thrombocytopenia are frequent adverse reactions of vinflunine. Complete blood counts should be checked before each vinflunine infusion.

The recommended dose should be reduced in patients with Grade > 3 haematological toxicity (see DOSAGE AND ADMINISTRATION).

Javlor should not be administered when the ANC is < 1.5 x 10^9/L and/or platelets < 100 x 10^9/L for the first administration and ANC < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L for subsequent administrations**.

Gastrointestinal disorders
Severe constipation (grade ≥ 3) occurred in 15.3% of treated patients. NCI CTC Grade 3 constipation is defined as “obstipation requiring manual evacuation or enema”. Grade 4 constipation is defined as “obstruction or toxic megacolon”. Constipation is reversible and can be prevented by special dietary measures such as oral hydration, fibre intake and the administration of laxatives such as stimulant laxatives or faecal softeners from day 1 to day 5 or 7 of the treatment cycle.

For patients at high risk of constipation (concomitant treatment with opiates, peritoneal carcinomas, abdominal masses, prior abdominal surgery), an osmotic laxative should be administered once a day from day 1 to day 7 in the morning before breakfast.

In the case of Grade 2 mucositis or constipation (defined as “requiring laxatives”) for 5 days or more or any Grade ≥ 3 gastrointestinal toxicity (except nausea or vomiting), the dose of vinflunine should be reduced (see DOSAGE AND ADMINISTRATION). Grade 2 is defined as “moderate”, Grade 3 as “severe” and Grade 4 as “life-threatening”.

During the phase I study involving cancer patients with renal impairment (RI), a case of fatal colonic perforation was seen in a patient with colorectal adenocarcinoma in the moderate RI group (n=13), 21 days after administration of vinflunine 280 mg/m^2. A sigmoid biopsy revealed massive necrosis of the colonic wall. Although this may have been the result of progressive disease, the role of vinflunine in this event cannot be excluded.**

Neuropathy
Neuropathy is a frequent adverse effect of vinflunine. Patients should be monitored for symptoms and signs of neuropathy before each vinflunine infusion. In the case of Grade 2 neuropathy (weakness or sensory disturbance not interfering with activities of daily living), the vinflunine dose should be reduced (see DOSAGE AND ADMINISTRATION). In the case of Grade ≥ 3 neuropathy (weakness or sensory

disturbance interfering with activities of daily living), vinflunine treatment should be discontinued.

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 increased proarrhythmic risk (e.g. congestive failure, known history of QT interval prolongation, hypokalemia) (see ADVERSE EFFECTS). The concomitant use of two or more QT/QTc interval prolonging substances is not recommended (see PRECAUTIONS – Interactions with other medicines).

Special attention is recommended when vinflunine is administered to patients with a prior history of myocardial infarction/ischemia or angina pectoris (see ADVERSE EFFECTS). Ischaemic cardiac events may occur, especially in patients who have underlying cardiac disease. Thus patients receiving vinflunine 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.

Venous irritation
When infused through a peripheral vein, vinflunine can induce Grade 1 (22.0% of patients, 14.1% of cycles), Grade 2 (11.0% of patients, 6.8% of cycles) or Grade 3 (0.8% of patients, 0.2% of cycles) venous irritation. All cases resolved rapidly without treatment discontinuation. Instructions for administration should be followed as described in “DOSAGE AND ADMINISTRATION – Administration of vinflunine”.

Posterior reversible encephalopathy syndrome (PRES)**
Cases of PRES have been observed after administration of vinflunine. The typical clinical symptoms are, with varying 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 resolve rapidly without sequelae after treatment discontinuation. Discontinuation of vinflunine should be considered in patients who develop neurological signs of PRES.

Hyponatraemia/Syndrome of inappropriate antidiuretic hormone secretion (SIADH)**
Cases of severe hyponatraemia/SIADH have been observed during treatment with vinflunine. Blood natraemia should be verified to identify severe hyponatraemia in

patients developing central nervous system disorders such as confusion, lethargy, altered consciousness associated or not with important fluid losses.

Special populations

Hepatic impairment

No modification of vinflunine and DVFL pharmacokinetics was observed in 25 patients with mild to moderate hepatic impairment compared to patients with normal hepatic function. This was further confirmed by a population pharmacokinetic analysis which demonstrated an absence of relationship between vinflunine clearance and biology markers of hepatic impairment. However, lower vinflunine doses are recommended in patients with mild to moderate hepatic impairment because the standard vinflunine dose was not tolerated (see DOSAGE AND ADMINISTRATION). Vinflunine is not recommended in severe hepatic impairment.

Renal impairment

A pharmacokinetic phase I study was performed in 2 groups of cancer patients with renal impairment (RI) classified according to the calculated creatinine clearance values: group 1 (n = 13 patients) with moderate impairment (40 mL/min ≤ creatinine clearance ≤ 60 mL/min) and group 2 (n = 20 patients) with severe impairment (20 mL/min ≤ creatinine clearance < 40 mL/min). The pharmacokinetic results of this study indicated a reduction of vinflunine clearance when creatinine clearance is decreased**. This was further confirmed by a population pharmacokinetic analysis which included 56 patients with a creatinine clearance between 20 mL/min and 60 mL/min which showed that vinflunine clearance is influenced by the creatinine clearance value (Cockcroft and Gault formula). Therefore the recommended dose should be reduced in patients with moderate and severe renal impairment (see DOSAGE AND ADMINISTRATION).

In the phase I study, increased rates of some adverse events were seen (compared to those listed in Table 2), in either one or both groups in terms of asthenia, constipation, anorexia, nausea and vomiting, abdominal pain, myalgia, arthralgia, diarrhoea and dehydration, leukopenia, neutropenia, thrombocytopenia and anaemia. One grade 4 myocardial infarction was observed in the severe RI group (n=20). A fatal colonic perforation in the moderate RI group (n=13) , 21 days after the administration of vinflunine 280 mg/m^2 was attributed to disease progression (colorectal adenocarcinoma); however the role of vinflunine in this case cannot be excluded. Due to small patient numbers in the study, the significance of these numbers is uncertain.

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 to < 75	17	320
75 to < 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 VFL were not modified for patients ≥ 70 and < 75 years old and patients ≥ 75 and < 80 years old.

Based on both PK and safety data, dose reductions are recommended in the elder groups: ≥ 75 and < 80 years old; and ≥ 80 years old. For further cycles, the dose should be adjusted in the event of toxicity (see DOSAGE AND ADMINISTRATION).

Paediatric use
The safety and effectiveness of vinflunine has not been established in patients below the age of 18 years. The subject indication does not apply to children.

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

Effects on fertility
There are no human data on the effects of vinflunine on male or female fertility. In animal studies, adverse effects on the male reproductive system of rats were observed at clinically-relevant systemic exposures. Both male and female patients with reproductive potential should take adequate contraceptive measures during treatment and for three months after the discontinuation of therapy. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinflunine.

Use in pregnancy
Category D

There are no data available on the use of vinflunine in pregnant women. Studies in rats and rabbits have shown embryotoxicity and teratogenicity at subclinical exposures. On the basis of the results of animal studies and the pharmacological action of vinflunine, 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.

Use in lactation
It is not known whether vinflunine or its metabolites are excreted in breast milk. In animal studies, adverse effects on postnatal development were seen in rat pups. Therefore, because of the potential harm to infants, breast feeding during treatment with vinflunine is contraindicated.

Carcinogenicity
The carcinogenic potential of vinflunine has not been studied. However, positive findings in genotoxicity assays suggest that vinflunine may have a carcinogenic potential.

Genotoxicity
Vinflunine was shown to be clastogenic (induces chromosome breakage) in a rat micronucleus test as well as mutagenic and clastogenic in mouse lymphoma assay. Negative results were obtained in bacterial mutagenicity assays (Ames test).

Interactions with other medicines
In vitro studies showed that vinflunine neither induced CYP1A2, CYP2B6 or CYP3A4 activity nor inhibited CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 activity.

In vitro studies showed that vinflunine is a Pgp-substrate like the other vinca alkaloids. The clinical relevance of this is unknown.

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 strong CYP3A4 inhibitor) on vinflunine pharmacokinetics indicated that co-administration of ketoconazole (400 mg p.o. once daily for 8 days) induced a 30% and 50% increase of both vinflunine and DVFL blood exposures 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 as they may increase or decrease vinflunine and DVFL concentrations.

The concomitant use of vinflunine with other QT/QTc interval prolonging drugs or pro-arrhythmic drugs should be avoided (see PRECAUTIONS – Cardiac disorders).

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 doxorubicinol metabolite concentrations were not affected. According to an *in vitro* study, such changes could be related to an adsorption of vinflunine to 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 (CYP3A 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 conducted.

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

Effects on ability to drive and operate machinery
The effect of vinflunine on the ability to drive and use machines has not been studied. However, patients should be advised not to drive or operate machinery if they experience any adverse reactions with a potential impact on their ability to perform these activities (e.g. dizziness and syncope are common).

ADVERSE EFFECTS

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

Adverse reactions are listed in Table 2 by System Organ Class, frequency and grade of severity (NCI CTC (National Cancer Institute Common Terminology Criteria) version 2.0).

Frequency of adverse reactions is defined as: very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10,000 and < 1/1000); very rare (< 1/10,000); and not known (cannot be estimated from available

data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: 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	3.8	3.8
		infections (viral, bacterial, fungal)	7.6	3.6
	Uncommon	neutropenic sepsis	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	1.8	0.2
Metabolism and nutrition disorders	Very common	hyponatraemia	39.8	11.7
		anorexia	34.4	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	6.0	0.4
		dysgeusia	3.3	0
		neuropathy	1.8	0
	Uncommon	peripheral motor neuropathy	0.7	0

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	**Grade 3 - 4**
		posterior reversible encephalopathy syndrome**	0.11	0.11
Eye disorders	Uncommon	visual disturbance	0.4	0
Ear and labyrinth disorders	Common	ear pain	1.3	0
	Uncommon	vertigo	0.9	0.4
		tinnitus	0.9	0
Cardiac Disorders	Very common	myocardial infarction	0.2[a]	0.2[a]
	Common	tachycardia	1.8	0.2
	Uncommon	myocardial ischaemia	0.7	0.7
Vascular Disorders	Common	hypertension	3.3	1.8
		vein thrombosis	3.6	0.4
		hypotension	1.1	0.2
		phlebitis	2.4	0
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
Gastro-intestinal Disorders	Very common	constipation	54.9	15.3
		abdominal pain	21.6	4.7
		vomiting	27.3	2.9
		nausea	40.9	2.9
		stomatitis	26.9	2.7
		diarrhoea	12.9	0.9
	Common	ileus	2.7	2.2
		dysphagia	2.0	0.4
		buccal disorders	4.7	0.2

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	**Grade 3 - 4**
		dyspepsia	5.6	0.2
	Uncommon	odynophagia	0.4	0.2
		gastric disorders	0.9	0
		oesophagitis	0.4	0.2
		gingival disorders	0.7	0
Neoplasm benign, malignant and unspecified.	Uncommon	Tumour pain	0.2	0.2
Skin and Subcutaneous Tissue Disorders	Very common	alopecia	28.9	NA
	Common	rash**	1.8	0
		urticaria**	1.3	0
		pruritus	1.3	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	2.2	0.9
		arthralgia	8.0	0.7
		back pain	4.9	0.4
		jaw pain	5.6	0
		pain in extremities	3.3	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	27.6	0.4
		pyrexia	10.9	0.4

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	**Grade 3 - 4**
	Common	chest pain	4.7	0.9
		chills	2.2	0.2
		pain	3.6	0.2
		oedema	1.3	0
	Uncommon	extravasation	0.7	0
Investigations	Very common	weight loss	24.0	0.4
	Uncommon	transaminases increased	0.4	0
		Weight gain	0.2	0

[a]see also *PRECAUTIONS, Special Populations, Renal Impairment*

Adverse reactions with a frequency below 1% reported in clinical trials in other indications

In other indications, the adverse reaction profile of vinflunine was similar to that in transitional cell carcinoma of the urothelium except for the following additional reactions:

Endocrine disorders
Uncommon: Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH).

Nervous System Disorders
Rare: Posterior Reversible Encephalopathy Syndrome

Post-Marketing experience

In addition to the adverse reactions reported during pre-registration clinical studies listed above, the following adverse drug reactions have been reported with post-marketing experience (frequency not known, cannot be estimated from the available data).

Nervous System Disorders: Posterior Reversible Encephalopathy Syndrome
Endocrine disorders: Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)**

DOSAGE AND ADMINISTRATION

Javlor Concentrated Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Before each cycle, adequate monitoring of complete blood counts should be conducted to verify the absolute neutrophil count (ANC) value, platelets and

haemoglobin as neutropenia, thrombocytopenia and anaemia are frequent adverse reactions of vinflunine**.

Recommended dose

The recommended dose is 320 mg/m^2 as a 20 minute intravenous infusion every 3 weeks.

For patients with WHO/ECOG performance status (PS) of 1 or prior pelvic irradiation, the treatment should be started at the dose of 280 mg/m^2. In the absence of any haematological toxicity during the first cycle causing treatment delay or dose reduction, the dose can be increased to 320 mg/m^2 every 3 weeks for subsequent cycles.

Dose adjustment due to toxicity

Table 3: Dose adjustment due to toxicity

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

***NCI CTC = National Cancer Institute Common Toxicity Criteria Version 2.0.**

[1] In the case of febrile neutropenia or neutropenia grade 4, consideration should be given to GCSF administration.

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

[3] NCI CTC Grade 3 nausea is defined as "no significant intake, requiring IV fluids". Grade 3 vomiting is defined as "≥ 6 episodes in 24 hours over pre-treatment; or need for IV fluids".

Dose delay or discontinuation due to toxicity

Table 4: Dose delay for subsequent cycles due to toxicity

Toxicity	Day 1 treatment administration
Neutropenia (ANC < 1 x 10^9/L) or Thrombocytopenia (platelets < 100 x 10^9/L).	Delay until recovery (ANC ≥ 1 x 10^9/L and platelets ≥ 100 x 10^9/L) and adjust the dose (see Table 3**). 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 3). Discontinuation if recovery has not occurred within 2 weeks**.
Neuropathy Grade ≥ 3	Discontinuation
Cardiac ischaemia in patients with a prior history of myocardial infarction or angina pectoris.	Discontinuation**

Dose adjustment in special populations

Hepatic impairment

Vinflunine pharmacokinetics are not modified in patients with mild to moderate hepatic impairment (see PRECAUTIONS, Special Populations**).** However, based on hepatic 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 of > 70% NV (normal value) and presenting with at least one of the following criteria: ULN (upper limit of normal) < bilirubin ≤ 1.5 x ULN and/or 1.5 x ULN < transaminases ≤ 2.5 x ULN and/or ULN < GGT ≤ 5 x ULN.

No dose adjustment is necessary in patients with transaminases ≤ 2.5 x ULN (< 5 x ULN only in the case of liver metastases).

The recommended dose of vinflunine is 250 mg/m^2 given once every 3 weeks in patients with mild liver dysfunction (Child-Pugh grade A) or in patients with a prothrombin time of ≥ 60% NV and 1.5 x ULN < bilirubin ≤ 3 x ULN and presenting with at least one of the following criteria: transaminases > ULN and/or GGT > 5 x ULN.

The recommended dose of vinflunine is 200 mg/m^2 given once every 3 weeks in patients with moderate liver dysfunction (Child-Pugh grade B) or in patients with a prothrombin time of ≥ 50% NV and bilirubin > 3 x ULN and transaminases > ULN and GGT > ULN.

Vinflunine has not been evaluated in patients with severe liver dysfunction such as patients with Child-Pugh Grade C, or patients with prothrombin time < 50% NV or with bilirubin > 5 x ULN or with isolated transaminases > 2.5 x ULN (≥5 x ULN only in the case of liver metastases) or with GGT > 15 x ULN.

Renal impairment

In the clinical studies, patients with creatinine clearance > 60 mL/min were included and treated at the recommended dose.

For patients with moderate renal impairment (40 mL/min ≤ creatinine clearance ≤ 60 mL/min), the recommended dose is 280 mg/m^2 given once every 3 weeks.

For patients with severe renal impairment (20 mL/min ≤ creatinine clearance < 40 mL/min), the recommended dose is 250 mg/m^2 given once every 3 weeks.

For further cycles, the dose should be adjusted in the event of toxicities, as shown in table 5 below.

Elderly (≥ 75 years)

No age-related dose modification is required in patients less than 75 years old (See PRECAUTIONS, Special Populations).

In patients at least 75 years old but less than 80 years, the recommended dose is 280 mg/m² every 3 weeks.

In patients 80 years or older, the recommended dose is 250 mg/m² every 3 weeks.

For further cycles, the dose should be adjusted in the event of toxicity, as shown in Table 5 below:

Table 5: Dose adjustment due to toxicity in renally impaired or elderly patients

Toxicity (NCI CTC v 2.0)*	**Dose adjustment**			
	Vinflunine initial dose of 280 mg/m²		**Vinflunine initial dose of 250 mg/m²**	
	First Event	2nd consecutive event	First Event	2nd consecutive event
Neutropenia Grade 4 (ANC < 0.5 x 10^9/L) > 7 days	250 mg/m²	Definitive treatment discontinuation	225 mg/m²	Definitive treatment discontinuation
Febrile neutropenia (ANC < 1 x 10^9/L and fever ≥ 38.5 °C)				
Mucositis or constipation grade 2 ≥ 5 days or ≥ 3 any duration[1]				
Any other toxicity grade ≥ 3				

(severe or life-threatening) (except Grade 3 vomiting or nausea[2])				

***NCI CTC = National Cancer Institute Common Toxicity Criteria Version 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 IV fluids. Grade 3 vomiting as ≥ 6 episodes in 24 hours over pretreatment, or need for IV fluids.

Administration

Javlor must be diluted prior to administration. Javlor is for single use only.

Javlor MUST ONLY be administered intravenously. Intrathecal administration of Javlor may be fatal. Javlor should be administered by a 20 minute intravenous infusion and should NOT be given by rapid intravenous bolus.

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 following each Javlor administration (see PRECAUTIONS – Gastrointestinal disorders).

General precautions for preparation and administration
As with other cytotoxic compounds, caution should be exercised when handling Javlor. Procedures for proper handling and disposal of anticancer medicines should be used. Several guidelines on this subject have been published.

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. If the Javlor solution comes in 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.

Javlor should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Javlor.

Dilution of the Javlor concentrate
The volume of Javlor concentrate corresponding to the calculated dose of Javlor should be mixed in a 100 mL bag of 0.9% Sodium Chloride Injection, USP (saline solution) or 5% Glucose Injection, USP (glucose solution).

To reduce microbiological hazard, Javlor should be used immediately after dilution. If storage is necessary, store at 2°C – 8°C for not more than 24 hours.

Administration of Javlor

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

The diluted solution of Javlor should be administered as follows:

- Venous access should be established for a 500 mL bag of saline/glucose solution in the upper part of the forearm or via the central venous arm line. The veins of the hand and those close to joints should be avoided.
- The intravenous infusion should be started with 100 mL of the 500 mL bag of saline/glucose solution at a free flowing rate to assess the patency of the vein.
- The Javlor solution should be piggy-backed to the side injection port closest to the 500 mL bag to further dilute Javlor during administration.
- The Javlor solution should be infused over 20 minutes.
- The flow rate of the saline/glucose solution during the Javlor infusion should be minimal (between 60 mL/h and 120 mL/h).
- The patency of the vein should be assessed frequently and extravasation precautions should be maintained throughout the infusion.
- After the Javlor infusion is completed, in order to adequately flush the vein, the remaining solution from the saline/glucose infusion bag (250 mL minimum) should be run at a flow rate of 300 mL/h.

Disposal

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

OVERDOSAGE

The main toxic effect of an overdose of vinflunine is bone marrow suppression with a risk of severe infection.

There is no known antidote for overdoses of vinflunine. In the case of an 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.

PRESENTATION

Javlor Concentrated Injection is a clear, colourless to pale yellow solution containing 25 mg vinflunine per mL. Javlor Concentrated Injection is available in 50 mg/2 mL, 100 mg/4 mL* and 250 mg/10 mL single use vials. It is packaged in clear glass vials (type 1), closed with a rubber stopper and sealed with an aluminium seal. Javlor Concentrated Injection is supplied in packs of 1 and 10 vials.

STORAGE CONDITIONS

Store at 2^{o}C to 8^{o}C (Refrigerate. Do not freeze)
Protect from light.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE

S4

DATE OF APPROVAL

11 February 2011

DATE OF MOST RECENT AMENDMENT

15 September 2014

* Not marketed

** *Please note changes in Product Information*

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