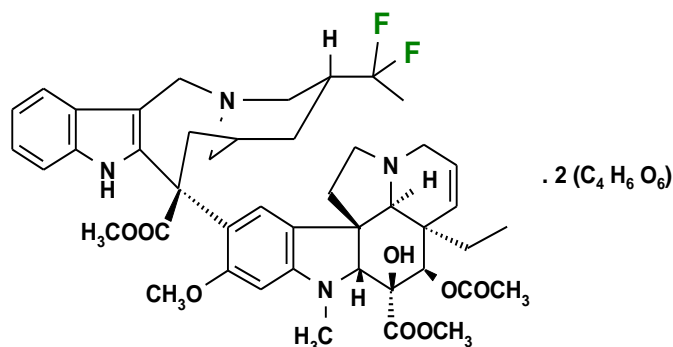


## NEW ZEALAND DATA SHEET

### 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<sub>53</sub>H<sub>66</sub>F<sub>2</sub>N<sub>4</sub>O<sub>20</sub> 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 xenographs in mice both in terms of survival prolongation and tumour growth inhibition.

## **Pharmacokinetics**

Vinflunine pharmacokinetics is linear up to 400 mg/m<sup>2</sup> 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 active metabolite and the main 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).

### Special populations

#### Hepatic impairment

No modification of vinflunine and DVFL pharmacokinetics was observed in 25 patients with varying degrees of 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, dose adjustment is recommended in patients with level 2 or 3 liver impairment (see DOSAGE AND ADMINISTRATION).

#### Renal impairment

A pharmacokinetic phase I study in patients with renal impairment is ongoing. An interim analysis on 13 patients with moderate impairment ( $40 \text{ mL/min} \leq \text{creatinine clearance} \leq 60 \text{ mL/min}$ ) and on 9 patients with severe impairment ( $20 \text{ mL/min} \leq \text{creatinine clearance} < 40 \text{ mL/min}$ ) indicated a decreased elimination of both vinflunine and DVFL when creatinine clearance is decreased. This was further confirmed by a population pharmacokinetic analysis which included 56 patients with a creatinine clearance between  $20 \text{ mL/min}$  and  $60 \text{ mL/min}$  which showed that vinflunine clearance is influenced by the creatinine clearance value (Cockcroft and Gault formula). Dosage adjustment is therefore recommended for patients with moderate and severe renal impairment (see DOSAGE AND ADMINISTRATION).

#### 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.

## **CLINICAL TRIALS**

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

In the two multi-centre open-label, single-arm phase II clinical trials, a total of 202 patients were treated with vinflunine. The overall objective response rates in evaluable patients as assessed by an independent review committee (IRC) were 17% in study VFL 202 and 15.9% in study CA 001. The disease control rates were 66.7% in study VFL 202 and 56.9% in study CA 001 and the duration of disease control was 4.6 months (study CA 001). 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.

The phase III clinical trial was an open-label, randomised, multi-centre study comparing Javlor 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 median overall survival in the intent to treat (ITT) population 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 with progression-free survival assessed by independent review: median progression-free survival was 3 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 (performance status (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 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); 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.

**Table 1: Summary of the clinical efficacy results for Javlor used as a single agent for the second-line treatment of patients with advanced or metastatic transitional cell carcinoma of the urothelial tract: 2 phase II studies (VFL 202 & CA 001) and 1 randomised phase III study (VFL 302).**

Results	VFL 202 (n=51)	CA 001 (n=151)	VFL 302 (Javlor + BSC) (n=253)	VFL 302 (BSC) (n=117)
Number of treated patients n (%)	51 (100)	151 (100)	248 (98)	117 (100)
ORR (IRP/IRRC/IRC) evaluable patients n (%) 95% CI	n = 47 8 (17.0) (7.6, 30.8)	n = 132 21 (15.9) (10.1, 23.3)	n = 185 16 (8.6) (5.0, 13.7)	n = 85 0
Disease control rate (%) IRP/IRRC/IRC 95% CI	34 (66.7) (52.1, 79.2)	86 (56.9) (48.7, 65.0)	104 (41.1) (35.0, 47.4)	29 (24.8) (17.3, 33.6)
Duration of disease control (months) 95% CI IRP/IRRC/IRC		4.6 (4.1, 5.5)	5.7 (5.0, 6.3)	4.2 (3.8, 4.9)
Median PFS (months) (investigators) (All randomised patients) 95% CI p-value	3.0 (2.4, 3.8) NA	2.7 (2.5, 2.8) NA	2.8 (2.4, 3.4)	1.4 (1.4, 1.5)
				p < 0.0001
Median PFS (months) (IRP/IRRC/IRC) (All randomised patients) 95% CI p-value	NA	2.8 (2.6, 3.8) NA	3.0 (2.1, 4.0)	1.5 (1.4, 2.3)
				p = 0.0012
Median OS (months) 95% CI All randomised patients p-value	NA	NA	n = 253 6.9 (5.7, 8.0)	n = 117 4.6 (4.1, 7.0)
				p = 0.2868
Median OS (months) 95% CI Eligible patients p-value	6.6 <sup>+</sup> (4.8, 7.6) NA	7.9 <sup>+</sup> (6.7, 9.7) NA	n = 249 6.9 (5.7, 8.0)	n = 108 4.3 (3.8, 5.4)
				p = 0.0403

+ : treated patients only

ORR = Objective response rate IRP = Independent radiological panel IRRC = Independent radiology review committee  
IRC = Independent review committee PFS = Progression free survival OS = Overall survival BSC = Best supportive care.

## INDICATIONS

Javlor is indicated as 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 Javlor have not been studied in patients with Performance Status  $\geq 2$ .

## **CONTRAINDICATIONS**

- Hypersensitivity to vinflunine or other vinca alkaloids.
- Recent (within 2 weeks) or current severe infection.
- Baseline absolute neutrophil count (ANC)  $< 1,500/\text{mm}^3$  or platelets  $< 100,000/\text{mm}^3$ .
- Lactation (see PRECAUTIONS – Use in lactation).

## **PRECAUTIONS**

### **Haematological toxicity**

Neutropenia is a frequent adverse reaction of vinflunine. Adequate monitoring of complete blood counts should be conducted to verify the ANC value 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  $< 1000/\text{mm}^3$  and/or platelets  $< 100,000/\text{mm}^3$ .

### **Gastrointestinal disorders**

Severe constipation occurred in 15.3% of treated patients. Constipation is reversible and not cumulative. To prevent constipation, special dietary measures such as oral hydration should be taken and laxatives should be administered 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), polyethylene glycol should be administered once a day from day 1 to day 7 in the morning before breakfast.

In the case of Grade 2 constipation for more than 5 days and Grade  $\geq 3$  of any duration, the dose of Javlor should be adjusted (see DOSAGE AND ADMINISTRATION).

For any Grade  $\geq 3$  gastrointestinal toxicity (except nausea or vomiting) and of mucositis (Grade 2 for more than 5 days and Grade  $\geq 3$  of any duration), dose adjustment is required (see DOSAGE AND ADMINISTRATION).

### **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 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 Javlor should be considered in patients who develop cardiac ischaemia.

### **Hepatic impairment**

The recommended dose should be reduced in patients with moderate or severe hepatic impairment (see DOSAGE AND ADMINISTRATION).

### **Renal impairment**

The recommended dose should be reduced in patients with moderate or severe renal impairment (see DOSAGE AND ADMINISTRATION).

### **Use in pregnancy**

Category D

There are no data available on the use of vinflunine in pregnant women. Studies in animals have shown embryotoxicity and teratogenicity. 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.

### **Fertility**

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.

### **Lactation**

It is not known whether vinflunine or its metabolites are excreted in breast milk. Therefore, because of the potential harm to infants, breast feeding during treatment with vinflunine is contraindicated.

### **Venous irritation**

When infused through a peripheral vein, Javlor 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 Javlor”.

### **Carcinogenicity**

The carcinogenic potential of vinflunine has not been studied.

### **Genotoxicity**

Vinflunine was shown to be clastogenic (induces chromosome breakage) in the *in vivo* micronucleus test in the rat as well as mutagenic and clastogenic in mouse lymphoma assay (without metabolic activation).

### **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, but with lower affinity. Therefore the risk of clinically significant interactions should be unlikely.

No pharmacokinetic interaction was observed in patients when vinflunine was combined with either cisplatin, carboplatin, capecitabine, doxorubicin or gemcitabine.

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 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 VFL 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 conducted.

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

### **Effects on ability to drive and operate machinery**

The effect of Javlor 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  and  $< 1/10$ ); uncommon ( $\geq 1/1000$  and  $< 1/100$ ); rare ( $\geq 1/10,000$  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
<b><i>Infections and infestations</i></b>	Common	neutropenic infection	3.8	3.8
		pneumonia	1.1	1.1
		urinary tract infection	1.6	0.4
	Uncommon	abscess	0.2	0.2
		bacteraemia	0.2	0.2
		bronchitis	0.4	0
		candidiasis	0.9	0
		catheter related infection	0.2	0.2
		cystitis	0.2	0
		Escherichia sepsis	0.2	0.2
		herpes virus infection	0.2	0
		infection	0.4	0.2
		nasopharyngitis	0.2	0
		neutropenic sepsis	0.2	0.2
		oral candidiasis	0.4	0
oral infection	0.4	0.2		

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
		pyelonephritis	0.2	0
		sepsis	0.2	0.2
		septic shock	0.2	0.2
		Upper respiratory tract infection	0.4	0
		wound infection	0.2	0
<b>Neoplasms benign and malignant (including cysts and polyps)</b>	Common	cancer pain	1.1	0.2
	Uncommon	metastatic pain	0.2	0
<b>Blood and lymphatic system disorders</b>	Very common	anaemia	92.8	17.3
		leucopenia	84.5	45.2
		neutropenia	79.6	54.6
		thrombocytopenia	53.5	4.9
	Common	febrile neutropenia	6.7	6.7
	Uncommon	disseminated intravascular coagulation	0.2	0.2
		pancytopenia	0.4	0.2
<b>Immune system disorders</b>	Common	hypersensitivity	1.8	0.2
	Uncommon	seasonal allergy	0.2	0
<b>Metabolism and nutrition disorders</b>	Very common	anorexia	34.4	2.7
	Common	dehydration	4.4	2.0
	Uncommon	acidosis	0.2	0
		gout	0.2	0
		hyperglycaemia	0.7	0.7
		hypoalbuminaemia	0.2	0
		hypoglycaemia	0.2	0.2
		hypomagnesaemia	0.4	0
		hypovolaemia	0.2	0.2

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
<b>Psychiatric disorders</b>	Common	anxiety	1.1	0
		insomnia	4.9	0.2
	Uncommon	confusional state	0.4	0.4
		depression	0.9	0
		disorientation	0.2	0.2
		restlessness	0.2	0
		sleep disorder	0.2	0
<b>Nervous system disorders</b>	Common	dizziness	5.3	0.4
		dysgeusia	2.9	0
		headache	6.2	0.7
		hypoesthesia	1.6	0
		neuralgia	6.0	0.4
		neuropathy	1.1	0
		paraesthesia	4.0	0.4
		peripheral sensory neuropathy	4.4	0.4
	Uncommon	ageusia	0.2	0
		convulsion	0.2	0.2
		depressed level of consciousness	0.2	0.2
		hyperaesthesia	0.2	0
		hypersomnia	0.2	0
		lethargy	0.4	0
		neuropathy peripheral	0.9	0
		peripheral motor neuropathy	0.7	0
		syncope	0.9	0.9
		syncope vasovagal	0.2	0.2
		tremor	0.4	0

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
<b>Eye disorders</b>	Uncommon	dry eye	0.2	0
		retinal vein thrombosis	0.2	0.2
		blurred vision	0.2	0
		Reduced visual acuity	0.2	0
		vitreous floaters	0.2	0
<b>Ear and labyrinth disorders</b>	Common	ear pain	1.3	0
	Uncommon	vertigo	0.7	0.4
		positional vertigo	0.2	0
		tinnitus	0.9	0
<b>Cardiac Disorders</b>	Uncommon	cardio-respiratory arrest	0.2	0.2
		myocardial ischaemia	0.7	0.7
		myocardial infarction	0.2	0.2
		palpitations	0.4	0
		sinus tachycardia	0.7	0.2
		supraventricular extrasystoles	0.2	0
		tachycardia	0.7	0
<b>Vascular Disorders</b>	Common	hypertension	3.3	1.8
		phlebitis	2.2	0
		hypotension	1.1	0.2
	Uncommon	arteriopathic disease	0.2	0
		deep vein thrombosis	0.4	0.4
		Flushing	0.4	0
		Hot flushes	0.2	0
		Hypovolaemic shock	0.2	0.2

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
		Ischaemia	0.2	0.2
		Lymphoedema	0.7	0
		Orthostatic hypotension	0.2	0.2
		Phlebitis superficial	0.2	0
		Thrombophlebitis	0.2	0
		Thrombophlebitis superficial	0.2	0
		vasculitis	0.2	0
		vasospasm	0.2	0
<b>Respiratory, thoracic and mediastinal disorders</b>	Common	cough	2.2	0
		dyspnoea	3.6	0.4
		epistaxis	1.1	0.2
	Uncommon	acute respiratory distress syndrome	0.2	0.2
		Cryptogenic organising pneumonia	0.4	0.2
		dysphonia	0.4	0
		dyspnoea exertional	0.7	0
		haemoptysis	0.2	0
		hiccups	0.4	0
		lung disorder	0.2	0
		pharyngolaryngeal pain	0.9	0
		pneumonitis	0.2	0
		productive cough	0.4	0
		pulmonary embolism	0.7	0.7
Pulmonary oedema	0.2	0.2		
<b>Gastro-</b>	Very common	abdominal pain	16.9	4.0

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
<i>intestinal Disorders</i>		constipation	54.9	15.3
		diarrhoea	12.9	0.9
		nausea	40.9	2.9
		stomatitis	26.9	2.7
		vomiting	27.3	2.9
	Common	Abdominal distension	1.1	0
		Upper abdominal pain	4.0	0.7
		Dry mouth	1.3	0
		dyspepsia	5.6	0.2
		dysphagia	2.0	0.4
		Flatulence	2.0	0
		ileus	2.4	2.2
		Oral pain	1.3	0.2
	Uncommon	abdominal discomfort	0.7	0.2
		lower abdominal pain	0.7	0
		anal haemorrhage	0.2	0
		colonic pseudo-obstruction	0.2	0.2
		epigastric discomfort	0.2	0
		eructation	0.4	0
		faecal incontinence	0.2	0
		faeces discoloured	0.2	0
		gastric ulcer haemorrhage	0.2	0
		gastritis	0.4	0
	gingival bleeding	0.2	0	
	gingival pain	0.4	0	

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
		glossodynia	0.4	0
		haematemesis	0.4	0.2
		haemorrhoids	0.7	0
		ileus paralytic	0.4	0.4
		intestinal obstruction	0.2	0
		Dry lips	0.2	0
		melaena	0.4	0.2
		mouth ulceration	0.2	0
		odynophagia	0.4	0.2
		oesophagitis	0.4	0.2
		oral discomfort	0.2	0
		Oral mucosal disorder	0.2	0
		Pancreatitis	0.2	0.2
		Paraesthesia oral	0.7	0
		Proctalgia	0.2	0
		Retching	0.4	0
		Altered saliva	0.2	0
		Small intestinal obstruction	0.2	0.2
		Subileus	0.2	0
		Swollen tongue	0.7	0
		Tongue blistering	0.2	0
toothache	0.2	0		
<b>Hepato-biliary disorders</b>	Uncommon	hepatic pain	0.2	0
<b>Skin and Subcutaneous Tissue Disorders</b>	Very common	alopecia	28.7	0
	Common	hyperhidrosis	1.1	0
		pruritus	1.3	0
		rash	1.6	0

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
		urticaria	1.3	0
	Uncommon	acne	0.2	0
		blisters	0.2	0
		Exfoliative dermatitis	0.2	0
		Dry skin	0.9	0
		erythema	0.4	0
		hypotrichosis	0.2	0
		Nail disorder	0.2	0
		Night sweats	0.2	0
		Skin pain	0.2	0
		Palmar-plantar erythrodysesthesia syndrome	0.2	0
		pigmentation disorder	0.2	0
		Pruritus generalised	0.2	0
		purpura	0.2	0
		Skin exfoliation	0.2	0
Skin lesion	0.2	0		
<b>Musculoskeletal and Connective Tissue Disorders</b>	Very common	myalgia	16.4	3.1
	Common	arthralgia	7.1	0.7
		back pain	4.9	0.4
		bone pain	2.4	0
		muscle spasms	1.8	0
		musculoskeletal chest pain	1.1	0.2
		musculoskeletal pain	2.0	0
		muscular weakness	2.2	0.9
		neck pain	1.6	0

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
		pain in extremities	3.3	0
		jaw pain	3.3	0.0
	Uncommon	flank pain	0.7	0
		groin pain	0.4	0.2
		joint stiffness	0.2	0
		muscle contracture	0.2	0
		Musculoskeletal stiffness	0.2	0
		trismus	0.2	0
<b>Renal and Urinary Disorders</b>	Uncommon	dysuria	0.4	0
		haematuria	0.9	0
		micturition disorder	0.2	0
		nocturia	0.2	0
		pollakiuria	0.2	0
		renal colic	0.2	0
		renal failure	0.2	0.2
<b>Reproductive system and breast disorders</b>	Common	pelvic pain	1.3	0.4
	Uncommon	penile discharge	0.2	0
		penile pain	0.2	0
<b>General Disorders and Administration Site Conditions</b>	Very common	fatigue	51.8	14.7
		injection site reaction	17.3	0.4
		pyrexia	10.9	0.4
	Common	asthenia	4.4	1.1
		chest pain	3.3	0.7
		chills	2.2	0.2
		infusion related reaction	1.1	0
		infusion site pain	2.2	0
		infusion site	1.1	0

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
		reaction		
		injection site erythema	1.3	0
		injection site irritation	1.3	0
		injection site pain	4.4	0
		Injection site phlebitis	2.4	0
		Peripheral oedema	1.1	0
	Uncommon	condition aggravated	0.2	0.2
		early satiety	0.2	0
		extravasation	0.7	0
		facial pain	0.2	0
		inflammation	0.2	0
		Influenza like illness	0.7	0
		Infusion site erythema	0.2	0
		Infusion site phlebitis	0.2	0
		Injection site hypersensitivity	0.2	0
		Injection site pruritis	0.7	0
		Injection site rash	0.4	0
		Injection site urticaria	0.4	0
		Malaise	0.4	0
		Non-cardiac chest pain	0.2	0
		oedema	0.2	0
		Peripheral coldness	0.2	0
<b>Investigations</b>	Very common	weight loss	24.0	0.4

System Organ Class	Frequency	Adverse Reactions	Worst NCI Grade per patient (%)	
			All grades	Grade 3 - 4
	uncommon	alanine aminotransferase increased	0.4	0
		aspartate aminotransferase increased	0.2	0
		electrocardiogram ST segment abnormal	0.2	0
		Neutrophil count increased	0.2	0.2
		Weight gain	0.2	0
<b><i>Injury, poisoning and procedural complications</i></b>	Uncommon	fall	0.7	0.2
		Ureterostomy site discomfort	0.2	0

## Adverse reactions in other indications

### Blood and lymphatic system disorders

Grade 3 and 4 neutropenia was observed in 49.6% of patients. Severe anaemia and thrombocytopenia were less common (respectively 10.3% and 3.5%). Febrile neutropenia defined as ANC < 1,000/mm<sup>3</sup> and fever ≥ 38.5°C of unknown origin without clinically microbiologically documented infection (NCI CTC version 2.0) was observed in 5.3% of patients. Infection with grade 3 and 4 neutropenia was observed in 3.0% of patients. Overall 7 patients (0.5% of the treated population) died from infection as a complication occurring during neutropenia.

### Gastrointestinal disorders

Constipation is a class effect of the vinca alkaloids: 12.0% of patients experienced severe constipation during treatment with vinflunine. Grade 3 and 4 ileus reported in 1.8% of patients was reversible when managed by medical care. Constipation was managed by medical care (see PRECAUTIONS - Gastrointestinal disorders).

### Nervous system disorders

Sensory peripheral neuropathy is a class effect of the vinca alkaloids. Grade 3 was experienced by 0.2% patients. All resolved during the study.

### Cardiovascular disorders

Cardiac effects are a known class effect of the vinca alkaloids. Myocardial infarction or ischemia were experienced by 0.5% of the patients. Most of these patients had a pre-existing cardiovascular disease or risk factors. One patient died after myocardial infarction and another 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 3.3% of the patients but was rarely severe (Grade 3 and 4: 1.2%). Bronchospasm was reported in one patient treated with vinflunine for a disease other than from transitional cell carcinoma of the urothelium.

### Eye disorders

One case of blurred vision and one case of reduced visual acuity have been reported.

### Endocrine disorders

Three cases of suspected Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) have been reported in patients treated with vinflunine for a disease other than transitional cell carcinoma of the urothelium.

## **DOSAGE AND ADMINISTRATION**

Javlor 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 as neutropenia is a frequent adverse reaction of vinflunine.

### **Recommended dose**

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

For patients with WHO/ECOG performance status (PS) of 1 or 0 and prior pelvic irradiation, the treatment should be started at the dose of 280 mg/m<sup>2</sup>. 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<sup>2</sup> every 3 weeks for subsequent cycles.

## Dose adjustment due to toxicity

**Table 3: Dose adjustment due to toxicity**

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

\*NCI CTC = National Cancer Institute Common Toxicity Criteria

In patients with ANC < 1,000/mm<sup>3</sup> or platelets < 100,000/mm<sup>3</sup> on the day of administration, the treatment should be delayed until recovery (ANC ≥ 1,000/mm<sup>3</sup> and platelets ≥ 100,000/mm<sup>3</sup>). If recovery has not occurred within 2 weeks, the treatment should be discontinued.

In the case of Grade 4 neutropenia (ANC < 500/mm<sup>3</sup>) for more than 7 days or febrile neutropenia, dose adjustment is recommended (see Table 3).

In the case of Grade ≥ 2 organ toxicity on the day of infusion, treatment should be delayed until recovery to Grade 0, 1 or initial baseline status.

### Dose adjustment in special populations.

#### Hepatic impairment

Vinflunine pharmacokinetics are not modified in patients with varying degrees of hepatic impairment (see Pharmacokinetics). However, based on hepatic parameter modifications following vinflunine administration (gamma glutamyl transferases (GGT), transaminases, bilirubin), the dose recommendations are as follows:

**Table 4: Dose adjustment for hepatic impairment**

Level and dose	Child Pugh Grade		Prothrombin time		Bilirubin		Transaminases		GGT
<u>Level 1</u> 320 mg/m <sup>2</sup>	-	-	> 70% NV	and	> ULN and ≤ 1.5 x ULN	and/or	> 1.5 x ULN and ≤ 2.5 x ULN	and/or	> ULN and ≤ 5 x ULN
<u>Level 2</u> 250 mg/m <sup>2</sup>	A	or	≥ 60% NV	and	> 1.5 x ULN and ≤ 3 x ULN	and	> ULN	and/or	> 5 x ULN
<u>Level 3</u> 200 mg/m <sup>2</sup>	B	or	≥ 50% NV	and	> 3 x ULN	and	> ULN	and	> ULN

**NV = Normal value      ULN = Upper limit of normal**

Vinflunine has not been evaluated in patients with more 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 transaminases > 6 x ULN or with gamma glutamyl transferases (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<sup>2</sup> 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<sup>2</sup> given once every 3 weeks.

**Elderly (> 65 years)**

In the clinical studies, 103 patients ≥ 75 years old and 374 patients ≥ 65 and < 75 years old were treated at the recommended dose of vinflunine. No significant difference in safety was observed between these two age groups. No specific dose recommendation is necessary in the elderly.

### Paediatric use

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

### **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 comedication

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 – 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 Javlor is bone marrow suppression with a risk of severe infection.

There is no known antidote for overdoses of Javlor. 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 to 8°C (Refrigerate. Do not freeze)  
Protect from light.

## **NAME AND ADDRESS OF THE SPONSOR**

New Zealand Medical & Scientific Limited  
2A Fisher Cres.  
Mt Wellington  
Auckland  
New Zealand  
Phone: 09 259 4062

## **MEDICINE CLASSIFICATION**

Prescription Medicine

## **DATE OF PREPARATION**

10 November 2009

\* Not marketed