

## CISplatin, Methotrexate and vinBLAStine Therapy

### INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Noadjuvant treatment of muscle invasive transitional cell carcinoma (TCC) of the urothelium	C67	00337a	Hospital

*\*If the reimbursement status is not defined, the indication has yet to be assessed through the formal HSE reimbursement process.*

### TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

Treatment is administered as described below every 21 days for a maximum of **3** cycles or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis **MUST** be present when the chemotherapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1,8	<sup>a</sup> VinBLAStine	4mg/m <sup>2</sup>	IV infusion	50ml 0.9% NaCl over 15 min	Every 21 days for up to 3 cycles
1,8	Methotrexate	30mg/m <sup>2</sup>	IV Bolus		Every 21 days for up to 3 cycles
2,9	Folinic acid	15mg	PO or IV	Every 6 hrs ( total 4 doses) to start 24hr after methotrexate on day 1 and day 8	Every 21 days for up to 3 cycles
2	<sup>b</sup> CISplatin	100mg/m <sup>2</sup>	IV infusion	500ml 0.9% NaCl over 120mins	Every 21 days for up to 3 cycles

<sup>a</sup>VinBLAStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer [Here](#)

#### <sup>b</sup> Pre and post hydration therapy required for CISplatin

See local hospital policy recommendations.

Suggested prehydration for CISplatin therapy:

- Administer 10mmol magnesium sulphate (MgSO<sub>4</sub>) ((+/-KCl 20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above

Post hydration: Administer 1000 ml 0.9% NaCl over 60mins

Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload (3,4).

### ELIGIBILITY:

- Indications as above
- ECOG 0-1

### EXCLUSIONS:

- Hypersensitivity to methotrexate, vinBLAStine, CISplatin or any of the excipients
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Pregnancy and Lactation
- Pre existing neuropathies ≥ grade 2
- Significant hearing impairment/tinnitus

NCCP Regimen: CISplatin, Methotrexate and VinBLAStine Therapy(CMV)-14 days	Published: 20/06/2016 Review: 20/06/2020	Version number: 2
Tumour Group: Genitourinary NCCP Regimen Code: 00337	ISMO Contributor: Prof Maccon Keane	Page 1 of 5

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician, and is subject to HSE's terms of use available at <http://www.hse.ie/eng/Disclaimer>

*This information is valid only on the day of printing, for any updates please check [www.hse.ie/NCCPchemoregimens](http://www.hse.ie/NCCPchemoregimens)*

## PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

## TESTS:

### Baseline tests:

- FBC, renal and liver profile
- Audiology and creatinine clearance if clinically indicated

### Regular tests:

- FBC, renal and liver profile prior to each cycle
- FBC and renal profile Day 8

### Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

## DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

## Haematological:

Table 1: Dose modification for haematological toxicity

ANC ( $\times 10^9$ /L)		Platelets ( $\times 10^9$ /L)	Dose
$\geq 1.5$	and	$\geq 100$	100% Dose
$< 1.5$	or	$< 100$	Hold* until recovery
Febrile neutropenia or ANC $< 0.5$	or	$< 50$	Hold *until recovery then 75% of previous dose
*Do not start a new cycles until ANC $\geq 1.5 \times 10^9$ /L and platelets $\geq 100 \times 10^9$ /L			

NCCP Regimen: Cisplatin, Methotrexate and VinBLASTine Therapy(CMV)-14 days	Published: 20/06/2016 Review: 20/06/2020	Version number: 2
Tumour Group: Genitourinary NCCP Regimen Code: 00337	ISMO Contributor: Prof Maccon Keane	Page 2 of 5
<p>The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician, and is subject to HSE's terms of use available at <a href="http://www.hse.ie/eng/Disclaimer">http://www.hse.ie/eng/Disclaimer</a></p> <p><i>This information is valid only on the day of printing, for any updates please check <a href="http://www.hse.ie/NCCPchemoregimens">www.hse.ie/NCCPchemoregimens</a></i></p>		

## Renal and Hepatic Impairment:

**Table 2: Dose modifications in renal and hepatic impairment**

Drug	Renal Impairment		Hepatic Impairment			
	Cr Cl (ml/min)	Dose	Bilirubin(micromol/L)		AST (Units)	Dose
Methotrexate	>80	100%	<50	and	<180	100%
	60	65%	51-85	or	>180	75%
	45	50%	>85			Contra-indicated
	<30	Contra-indicated				
vinBLASTine	No dose reduction necessary		Bilirubin(micromol/L)		AST/ALT(Units)	Dose
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	Omit
CISplatin	CrCl (ml/min)	Dose	No dose reduction necessary			
	≥60	100%				
	45-59	75%				
	<45	Consider CARBOplatin				

## Management of adverse events:

**Table 3: Dose Modification of CMV Therapy for Adverse Events**

Adverse reactions	Recommended dose modification
<b>Neurotoxicity</b> Grade 2 present at start of next cycle  Grade 3	Reduce dose of CISplatin and vinBLASTine by 25% dose.  Discontinue CISplatin and vinBLASTine

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

CISplatin	High
Methotrexate	Low
vinBLASTine	Minimal ( <b>Refer to local policy</b> ).

**PREMEDICATIONS:** None usually required

### OTHER SUPPORTIVE CARE:

- Hydration prior and post CISplatin administration (**Reference local policy or see recommendations above**). Patient should be encouraged to drink large quantities of liquids for 24 hours after the CISplatin infusion to ensure adequate urine secretion.
- Prophylactic laxatives may be required to prevent constipation related to the use of vinca alkaloids.

NCCP Regimen: CISplatin, Methotrexate and VinBLASTine Therapy(CMV)-14 days	Published: 20/06/2016 Review: 20/06/2020	Version number: 2
Tumour Group: Genitourinary NCCP Regimen Code: 00337	ISMO Contributor: Prof Maccon Keane	Page 3 of 5
<p>The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician, and is subject to HSE's terms of use available at <a href="http://www.hse.ie/eng/Disclaimer">http://www.hse.ie/eng/Disclaimer</a></p> <p><i>This information is valid only on the day of printing, for any updates please check <a href="http://www.hse.ie/NCCPchemoregimens">www.hse.ie/NCCPchemoregimens</a></i></p>		

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Pleural effusion or ascites:** Methotrexate should be used with caution in patients with pleural effusions or ascites, as methotrexate may accumulate in third space fluid compartments.
- **Extravasation:** vinBLAStine is a vesicant. DOXOrubicin may cause pain and tissue necrosis if extravasated. (Refer to local extravasation guidelines).
- **Hypersensitivity:** Hypersensitivity reactions have been reported with CISplatin.
- **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used, monitor renal function.
- **Ototoxicity and sensory neural damage:** These are associated with CISplatin therapy. They should be assessed by history prior to each cycle

## DRUG INTERACTIONS:

- NSAIDs may decrease the clearance of methotrexate by decreasing its renal perfusion and tubular secretion thus increasing its toxicity.
- Sulphonamides and penicillins may displace bound methotrexate from plasma protein increasing serum methotrexate levels and its toxicity.
- Concomitant administration of drugs that cause folate deficiency may lead to increased methotrexate toxicity.
- Ciprofloxacin may inhibit renal tubular transport of methotrexate, increasing serum methotrexate levels and its toxicity.
- Probenecid may inhibit renal excretion of methotrexate, increasing serum methotrexate levels and its toxicity.
- Co-administration of CISplatin has been reported to cause higher plasma concentrations of vinBLAStine.
- Erythromycin may increase the toxicity of vinBLAStine.
- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Current drug interaction databases should be consulted for more information.

## ATC CODE:

Methotrexate	-	L01BA01
vinBLAStine	-	L01CA01
CISplatin	-	L01XA01

## REFERENCES:

1. International Collaboration of Trialists. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol. 2011;29(16):2171-2177.

NCCP Regimen: CISplatin, Methotrexate and VinBLAStine Therapy(CMV)-14 days	Published: 20/06/2016 Review: 20/06/2020	Version number: 2
Tumour Group: Genitourinary NCCP Regimen Code: 00337	ISMO Contributor: Prof Maccon Keane	Page 4 of 5
<p>The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician, and is subject to HSE's terms of use available at <a href="http://www.hse.ie/eng/Disclaimer">http://www.hse.ie/eng/Disclaimer</a></p> <p><i>This information is valid only on the day of printing, for any updates please check <a href="http://www.hse.ie/NCCPchemoregimens">www.hse.ie/NCCPchemoregimens</a></i></p>		

2. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. *Lancet*. 1999;354(9178):533
3. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3  
<https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-prevention/184-nephrotoxicity-associated-with-CISplatin>
4. Portilla D et al. CISplatin nephrotoxicity. UptoDate Accessed Oct 2017  
[https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search\\_result&search=CISplatin%20hydration&selectedTitle=1~150](https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150)
5. Methotrexate Summary of Product Characteristics Accessed June 2018  
Available at [http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC\\_PA0437-005-003\\_22042013144145.pdf3](http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0437-005-003_22042013144145.pdf3).
6. Vinblastine Sulfate 1mg/ml Solution for Injection. Accessed June 2018. Available at  
[http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC\\_PA0437-009-003\\_20012016143038.pdf](http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0437-009-003_20012016143038.pdf)
7. Cisplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Accessed June 2018. Available at  
[http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC\\_PA0749-119-002\\_06062013115044.pdf](http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0749-119-002_06062013115044.pdf)

Version	Date	Amendment	Approved By
1	20/06/2016		Prof Maccon Keane
2	20/06/2018	Updated with new NCCP regimen format, standardisation of treatment table updated with revised CISplatin hydration regimen recommendations	Prof Maccon Keane

Comments and feedback welcome at [oncologydrugs@cancercontrol.ie](mailto:oncologydrugs@cancercontrol.ie).

<sup>i</sup> ODMS – Oncology Drug Management System

CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes

Further details on the Cancer Drug Management Programme is available at;

<http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/>

NCCP Regimen: CISplatin, Methotrexate and VinBLASTine Therapy(CMV)-14 days	Published: 20/06/2016 Review: 20/06/2020	Version number: 2
Tumour Group: Genitourinary NCCP Regimen Code: 00337	ISMO Contributor: Prof Maccon Keane	Page 5 of 5
<p>The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician, and is subject to HSE's terms of use available at <a href="http://www.hse.ie/eng/Disclaimer">http://www.hse.ie/eng/Disclaimer</a></p> <p><i>This information is valid only on the day of printing, for any updates please check <a href="http://www.hse.ie/NCCPchemoregimens">www.hse.ie/NCCPchemoregimens</a></i></p>		