CARBOplatin and Vinorelbine Therapy-21 Day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of locally advanced, recurrent or metastatic non-small cell lung cancer (NSCLC) in patients not suitable for treatment with CISplatin	C34	00614a	N/A

* This is for post 2012 indications only.

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 patients individual clinical circumstances.

CARBOplatin is administered on day 1 and vinorelbine is administered on days 1 and 8 of a 21 day cycle for 4 cycles or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when systemic anti cancer therapy (SACT) is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 8	[a,b]Vinorelbine	25mg/m^2	IV infusion	50mL 0.9% NaCl over 15 minutes. Then flush the line with 250mL 0.9% NaCl prior to removing/ capping IV access.	Every 21 days for 4 cycles
2	1	CARBOplatin	AUC 5	IV infusion	500mL glucose 5% over 30 minutes	Every 21 days for 4 cycles

[a]Vinorelbine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer. Available on the NCCP website

[b]Vinorelbine dose may be initiated or increased to 35 mg/m^2 at the treating physician's discretion.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

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AlTERNATIVE TREATMENT TABLE CARBOplatin and vinorelbine therapy (Oral vinorelbine)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 8	Vinorelbine[a,b,c,d]	60mg*/m^2 once weekly **(MAX 120mg)**	PO	N/A	Every 21 days for 4 cycles
2	1	CARBOplatin	AUC 5	IV infusion	500mL glucose 5% over 30 minutes	Every 21 days for 4 cycles

* If well tolerated consider increasing the dose of vinorelbine to 80mg/m^2 from cycle 2 or 3.

[a]Swallow whole with water, without chewing, sucking or dissolving capsule. It is recommended to administer the capsule with some food

[b]If the patient chews or sucks the capsule by error, the liquid is an irritant. Proceed to mouth rinses with water or preferably a normal saline solution. In the event of the capsule being cut or damaged, the liquid content is an irritant, and so may cause damage if in contact with skin, mucosa or eyes. Damaged capsules should not be swallowed and should be returned to the pharmacy or to the doctor in order to be properly destroyed. If any contact occurs, immediate thorough washing with water or preferably with normal saline solution should be undertaken.

[c]In the case of vomiting within a few hours after drug intake, do not re-administer.

[d]Vinorelbine is commonly available as 20mg, 30mg and 80mg capsules.
30mg/ m^2 IV is equivalent to 80mg/m^2 PO and 25mg/m^2 IV is equivalent to 60mg/ m^2 PO.

Table 1: Dose of vinorelbine (PO) required for appropriate ranges of body surface area (BSA).

	60mg/m^2	80mg/m^2
BSA (m^2)	Dose (mg)	Dose (mg)
0.95 to 1.04	60	80
1.05 to 1.14	70	90
1.15 to 1.24	70	100
1.25 to 1.34	80	100
1.35 to 1.44	80	110
1.45 to 1.54	90	120
1.55 to 1.64	100	130
1.65 to 1.74	100	140
1.75 to 1.84	110	140
1.85 to 1.94	110	150
≥1.95	120	160

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/mL x min) x (GFR mL/min +25)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible.

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- **Estimation of GFR** (eGFR) can be done by using the Wright formula or using the Cockcroft and Gault formula to measure creatinine clearance
- The GFR used to calculate the AUC dosing should not exceed 125mL/minute.
  - For obese patients and those with a low serum creatinine, for example, due to low body weight or post-operative asthenia, estimation using formulae may not give accurate results; measured GFR is recommended.
    - where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight in the Cockcroft and Gault formula may be considered.
    - where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered.

These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (mL/min)} = \frac{6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (µmol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (mL/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (µmol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\textbf{GFR (ml/min)} = \frac{\textbf{S x (140 - age in years) x wt (kg)}}{\textbf{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

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ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate hematologic, hepatic and renal function

EXCLUSIONS:

- Hypersensitivity to vinorelbine or other vinca alkaloids, CARBOplatin* or any of the excipients
- Pregnancy
- Lactation
- Patients requiring long term oxygen therapy

*If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision

USE with CAUTION:

- Disease significantly affecting absorption
- Previous significant surgical resection of stomach or small bowel

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Peripheral neuropathy assessment
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Peripheral neuropathy assessment prior to each cycle

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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 2: Dose modification of CARBOplatin and vinorelbine in haematological toxicity

ANC (x 10^9/L)	
0.5 to < 1.0	Delay treatment until recovery
< 0.5	Delay treatment until recovery and reduce vinorelbine and CARBOplatin by 25% for subsequent cycles
Febrile neutropenia	Delay treatment until recovery and reduce vinorelbine and CARBOplatin by 25% for subsequent cycles
Prolonged recovery greater than two weeks delay, or 3rd delay for myelosupression	Delay treatment until recovery and reduce vinorelbine and CARBOplatin by 50% for subsequent cycles or cease
Platelets (x 10^9/L)	
50 to <100	Delay treatment until recovery
<50	Delay treatment until recovery and reduce vinorelbine and CARBOplatin by 25% for subsequent cycles

Renal and Hepatic Impairment:

Table 3: Dose modification of CARBOplatin and vinorelbine in renal and hepatic impairment

Drug	**Renal Impairment**	**Hepatic Impairment**	
CARBOplatin[a]	See note below*	No dose modification required	
Vinorelbine[b]	No dose adjustment is needed. Haemodialysis: no need for dose adjustment is expected.	**Mild and moderate**	No dose adjustment is needed.
		Severe	Consider 66% of original dose.
[a] Renal – see note below*, hepatic – Giraud et al 2023 [b] Giraud et al 2023			

***Renal dysfunction and CARBOplatin:**

- Patients with creatinine clearance values of < 60mL/minute are at greater risk to develop myelosuppression.
- In case of GFR ≤ 20mL/minute , CARBOplatin should not be administered at all.

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- If Cockcroft & Gault or Wright formulae are used, the dose should be calculated as required per cycle based on a serum creatinine obtained within 48 hours of drug administration.
- If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to remeasuring the GFR or to recalculating using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 4: Dose Modifications for Adverse Events

Adverse reactions	Recommended dose modification
Peripheral neuropathy	
Grade 2 which is present at start of next cycle	Reduce vinorelbine by 25%; if persistent, reduce vinorelbine by 50%
Grade 3 or grade 4	Omit vinorelbine
Mucositis and stomatitis	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce dose for subsequent cycles as follows: 1st occurrence: No dose reduction 2nd occurrence: Reduce CARBOplatin and vinorelbine by 25% 3rd occurrence: Reduce CARBOplatin and vinorelbine by 50% 4th occurrence: Omit CARBOplatin and vinorelbine
Grade 3 or grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: Reduce CARBOplatin and vinorelbine by 50% 2nd occurrence: Omit CARBOplatin and vinorelbine

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website :

CARBOplatin: High (**Refer to local policy).**
Vinorelbine: Minimal (**Refer to local policy).**

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by

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aprepitant.

PREMEDICATIONS:

Not usually required

OTHER SUPPORTIVE CARE:

- Patients should be counseled on the risk of constipation associated with the use of vinca alkaloids. Dietary interventions or prophylactic laxatives may be required.
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

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2. Horvath, L., M. Boyer, S. Clarke, et al. 2001. Carboplatin and vinorelbine in untreated locally advanced and metastatic non-small cell lung cancer. Lung Cancer. 32(2):173-178.
3. Tan, E. H., A. Szczesna, M. Krzakowski, et al. 2005. Randomized study of vinorelbine--gemcitabine versus vinorelbine--carboplatin in patients with advanced non-small cell lung cancer. Lung Cancer 49(2):233-240.
4. Depierre A, Freyer J et al. Oral vinorelbine: Feasibility and safety profile Annals of Oncology 2001;12: 1677-1681
5. Ekhart C, Rodenhuis S et al. Carboplatin dosing in overweight and obese patients with normal renal function, does weight matter? Cancer Chemother Pharmacol 2009;64:115-122.
6. Wright JG, Boddy AV, et al, Estimation of glomerular filtration rate in cancer patients. British Journal of Cancer 2001; 84(4):452-459
7. Appropriate chemotherapy dosing for obese adult patients with cancer:American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2012; 30 (13) 1553-1561.
8. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext

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9. NCCN CARBOplatin dosing in adults https://www.nccn.org/docs/default-source/clinical/order-templates/appendix_b.pdf?sfvrsn=6286822e_6
10. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
11. Vinorelbine 10 mg/ml Concentrate for Solution for Infusion SmPC. Last updated 18/12/2013. Accessed July 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1226-010-001_18122013162040.pdf
12. Vinorelbine (Navelbine®) 20mg soft capsule. SmPC. Last updated 08/01/2024. Accessed July 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0329-011-001_08012024110935.pdf
13. CARBOplatin 10mg/ml Concentrate for Solution for Infusion.SmPC. Last updated 2018 . Accessed July 2024 . Available at: https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0437-017-002A_25062018161037.pdf

Version	Date	Amendment	Approved By
1	02/12/2020		Prof Maccon Keane
2	02/09/2022	Updated CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing and creatinine value. Updated baseline tests. Updated Dose modification of CARBOplatin in haematological toxicity Updated emetogenic potential..	Prof Maccon Keane
3	15/05/2023	Updated emetogenic potential section and drug interactions section	Prof Maccon Keane
4	09/12/2024	Addition of alternative PO treatment tables. Addition of Table 1. Addition of cautions section. Updated exclusions section. Updated renal and hepatic dose modifications section for vinorelbine to align to Giraud et al. Regimen updated to align with NCCP standardisation	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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