CARBOplatin (AUC5) and Etoposide 100mg/m^2 Therapy-21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Small cell lung cancer (SCLC) extensive disease	C34	00271a	Hospital

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 etoposide is administered on three consecutive days (Days 1-3) of a 21 day cycle for 4-6 cycles or until disease progression or unacceptable toxicity develops.
Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Table 1: Treatment Schedule for CARBOplatin (IV) and Etoposide (IV)

Order of Admin	Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1	1	CARBOplatin	AUC 5	IV infusion	500ml glucose 5% over 30 mins	Every 21 days
2	1-3	Etoposide	100mg/m^2	IV Infusion*	1000ml 0.9% NaCl over 60 mins	Every 21 days

*See alternate treatment schedule using IV and PO etoposide below.

ALTERNATE TREATMENT SCHEDULE:

CARBOplatin (AUC 5) + Etoposide (Day 1 IV, Day 2 & 3 oral) Therapy-21 day

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 etoposide is administered as an IV infusion on Day 1 and then administered as PO doses on Days 2 and 3 of a 21 day cycle for 4-6 cycles or until disease progression or unacceptable toxicity develops according to the table below.

Table 2: Alternate Treatment Schedule for CARBOplatin (IV) and Etoposide (IV and PO)

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	CARBOplatin	AUC 5	IV Infusion	500ml glucose 5% over 30 mins	Every 21 days
2	1	Etoposide	100mg/m^2	IV Infusion	1000ml 0.9% NaCl over 60 mins	Every 21 days
1	2, 3	Etoposide	[a]100mg/m^2 twice daily	PO		Every 21 days

[a]Etoposide is available in 50mg and 100mg capsules. The capsules should be taken on an empty stomach.

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.
- **Estimation of GFR** (eGFR) may be performed using the Wright formula to estimate GFR or the Cockcroft and Gault formula to estimate creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- 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*.

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

2. *SCr measured using Jaffe assay*

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

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

COCKCROFT-GAULT FORMULA

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

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indications as above
- Patients unsuitable for treatment with CISplatin based regimens
- ECOG 0-2 (0-3 in patients < 70)

EXCLUSIONS:

- Hypersensitivity to CARBOplatin, etoposide or any of the excipients
- Pregnancy or breast feeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

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

Regular tests:

- FBC weekly prior to treatment
- Renal and liver profile prior to each cycle

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 3: Dose modifications for haematological toxicity on Day 1

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥ 1.5	**And**	≥ 100	100%
< 1.5	**and/or**	< 100	Delay one week or until recovery
< 0.5 for > 5days or neutropenic fever			Consider dose reduction for etoposide

Renal and Hepatic Impairment:

Table 4: Dose modification of CARBOplatin and etoposide in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="4">Hepatic Impairment</th></tr>
<tr><td>CARBOplatin</td><td colspan="2">Patients with creatinine clearance values of <60ml/min are at greater risk to develop myelosuppression.
In case of GFR ≤ 20ml/min CARBOplatin should not be administered at all.
If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required per cycle based on a serum creatinine obtained within 48 hrs 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</td><td colspan="4">Probably no dose modification required</td></tr>
<tr><td rowspan="4">Etoposide</td><td>CrCl (ml/min)</td><td>Dose</td><td>Bilirubin (micromol/L)</td><td></td><td>AST (Units/L)</td><td>Dose Etoposide</td></tr>
<tr><td>>50</td><td>100%</td><td>26-51</td><td>or</td><td>60-180</td><td>50%</td></tr>
<tr><td>15-50</td><td>75%</td><td>>51</td><td>or</td><td>>180</td><td>Clinical decision</td></tr>
<tr><td><15</td><td>50%</td><td colspan="4" rowspan="2"></td></tr>
<tr><td colspan="2">Subsequent dosing should be based on patient tolerance and clinical effect.</td></tr>
</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CARBOplatin	High (**Refer to local policy).**
Etoposide	Low (**Refer to local policy).**

PREMEDICATIONS:

None usually required unless patient has experienced a previous hypersensitivity reaction.

OTHER SUPPORTIVE CARE: No specific recommendations

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.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.
- **Hypersensitivity:** High risk with etoposide and CARBOplatin. Hypersensitivity risk increases with number of cycles of CARBOplatin.

DRUG INTERACTIONS:

- Avoid concurrent use of CARBOplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use of CARBOplatin with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). If necessary perform regular audiometric testing.
- CYP3A4 inducers may increase the clearance of etoposide.
- CYP3A4 and p-gp inhibitors may decrease the clearance of etoposide
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Rossi, A., M. Di Maio, P. Chiodini, et al. CARBOplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol 2012; 30(14):1692-1698
2. Kosmidis, P. A., E. Samantas, G. Fountzilas, et al. Cisplatin/etoposide versus CARBOplatin/etoposide chemotherapy and irradiation in small cell lung cancer: a randomized phase III study. Hellenic Cooperative Oncology Group for Lung Cancer Trials. Semin.Oncol.1994; 21(3 Suppl 6):23-30.

3. Skarlos, D. V., E. Samantas, P. Kosmidis, et al.Randomized comparison of etoposide-cisplatin vs. etoposide-CARBOplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. Ann.Oncol 1994;5(7):601-607.
4. Okamoto H, Watanbe K et al. Randomised phase III trial of CARBOplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. Br J Cancer. 2007; 97(2): 162–169
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. NCCN CARBOplatin dosing in adults https://www.nccn.org/docs/default-source/clinical/order-templates/appendix_b.pdf?sfvrsn=6286822e_6
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. Wright JG, Boddy AV, et al, Estimation of glomerular filtration rate in cancer patients. British Journal of Cancer 2001; 84(4):452-459
9. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
10. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
11. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. 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
12. CARBOplatin Summary of Product Characteristics Last updated: 2018. Accessed Aug 2022. Available at: https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0437-017-002A_25062018161037.pdf
13. Etoposide 20 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics. HPRA Last updated: 17/05/2021. Accessed Aug 2022. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-036-001_17052021114619.pdf

Version	Date	Amendment	Approved By
1			Prof Maccon Keane
2	06/12/2017	Updated with new NCCP regimen template. Title amended to include dose. Emetogenic status CARBOplatin amended from moderate to moderate to high	Prof Maccon Keane
3	20/11/2019	Reviewed. Standardisation of treatment table and renal dose modifications. Update of emetogenic potential.	Prof Maccon Keane
4	30/08/2022	Updated CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing and creatinine value. Updated baseline tests. Updated dose modifications for haematological.	Prof Maccon Keane
5	24/03/2023	Added alternate treatment schedule to include PO etoposide	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.