Serplulimab, CARBOplatin AUC5 and Etoposide 100mg/m^2 – 21 Day Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
In combination with CARBOplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).	C34	00908a	N/A

* This applies to post 2012 indications

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.

Induction phase: Serplulimab and CARBOplatin are administered on day 1 and etoposide is administered on Days 1, 2 and 3 of a 21 day cycle, for 4 cycles unless the patient experiences disease progression or unacceptable toxicity.

Maintenance phase: The induction phase is followed by a maintenance phase without chemotherapy during which serplulimab is administered every 3 weeks unless the patient experiences disease progression or unacceptable toxicity.

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

There are different formulations available for etoposide. Please refer to Tables 2 below that outline the alternative treatment schedule.

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

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Serplulimab	4.5mg/kg	IV infusion	250ml NaCl 0.9% over 100mL/hour[a,b] using a sterile, non-pyrogenic, low-protein binding 0.2-5.0 micron in-line or add-on filter	Every 21 days
2	1	CARBOplatin	AUC 5	IV infusion	500mL Glucose 5% over 30 minutes	Every 21 days for 4 cycles only
3	1,2,3	Etoposide	100mg/m^2	IV infusion*	1000mL NaCl 0.9% over 60 minutes	Every 21 days for 4 cycles only
[a]The initial infusion rate should be set up to 100mL per hour. If the first infusion is well tolerated, all subsequent infusions may be given over 30 minutes (+/- 10 minutes). The infusion rate can be adjusted if infusion-related reactions occur.						
[b]The final concentration should between 1mg/mL and 8 mg/mL.						
*See alternative treatment schedule for Etoposide PO below (Table 2).						

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

ALTERNATIVE TREATMENT SCHEDULE

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Serplulimab	4.5mg/kg	IV infusion	250ml NaCl 0.9% over 100mL/hour[a,b] using a sterile, non-pyrogenic, low-protein binding 0.2-5.0 micron in-line or add-on filter	Every 21 days
2	1	CARBOplatin	AUC 5	IV infusion	500mL Glucose 5% over 30 minutes	Every 21 days for 4 cycles only
3	1	Etoposide	100mg/m^2	IV infusion*	1000mL NaCl 0.9% over 60 minutes	Every 21 days for 4 cycles only
1	2, 3	Etoposide[c]	100mg/m^2 twice daily	PO		Every 21 days for 4 cycles only
[a]The initial infusion rate should be set up to 100mL per hour. If the first infusion is well tolerated, all subsequent infusions may be given over 30 minutes (+/- 10 minutes). The infusion rate can be adjusted if infusion-related reactions occur.						
[b]The final concentration should between 1mg/mL and 8 mg/mL.						
[c]Etoposide is available in 50mg and 100mg capsules. The capsules should be taken on an empty stomach.						

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

CARBOplatin dose:

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

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

- Measured GFR (e.g. nuclear renogram) is preferred whenever feasible
- Estimation of GFR 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/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:

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

2. SCr measured using Jaffe assay:

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

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

COCKCROFT-GAULT FORMULA:

$$\text{GFR (mL/minute)} = \frac{\text{S} \times (140 - \text{age in years}) \times \text{weight (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indication as above
- ECOG status 0-2
- Adequate haematological, hepatic and renal function
- Baseline ANC ≥1.5 x 10^9/L and platelets ≥100 x 10^9/L

CAUTIONS:

- Immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisoLONE/daily (or steroid equivalent, excluding inhaled or topical steroids
- Untreated central nervous system (CNS) metastases
- Any active clinically significant infection requiring therapy
- Symptomatic interstitial lung disease

EXCLUSIONS:

- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody is Available on the NCCP website
- Hypersensitivity to serplulimab, CARBOplatin*, etoposide or any of the excipients
- Pregnancy or breastfeeding

*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

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose
- Thyroid function tests (TFTs)
- Isotope GFR measurement (preferred) or GFR / CrCl estimation
- Audiology referral as clinically indicated

Regular tests:

- FBC, liver, renal and glucose profile prior to each cycle
- TFTs every 3 to 6 weeks
- Lipid profile as clinically indicated
- ECG as clinically indicated
- Cortisol as clinically indicated
- Audiology referral as clinically indicated

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
- Serplulimab:
    - Dose escalation or dose reductions are not recommended
    - Treatment may be interrupted or discontinued due to toxicity. Please refer to Table 5 below for treatment modification. Dose withholding for up to 12 weeks for tolerability is acceptable
- CARBOplatin and etoposide:
    - Dose modifications are permitted for CARBOplatin and etoposide to manage haematological toxicities and renal and hepatic impairment. Please refer to Tables 3 below.

Haematological:

Table 3: Dose modification of CARBOplatin and etoposide in haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥1.0	and	≥100	100%
0.5 to <1.0	and/or	75 to <100	Delay one week until recovery
<0.5 or neutropenic fever	and/or	<50	Delay and consider dose reduction for CARBOplatin and etoposide dose by 25%

Renal and Hepatic Impairment:

Table 4: Dose modification in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="2">Hepatic Impairment</th></tr>
<tr><td rowspan="3">Serplulimab[a]</td><td>CrCl (mL/min)</td><td>Dose</td><td>Impairment level</td><td>Dose</td></tr>
<tr><td>≥30</td><td>No dose adjustment is needed</td><td>Mild
Bilirubin ≤ULN and AST > ULN or
Bilirubin >1-1.5 X ULN and any AST</td><td>No dose adjustment needed</td></tr>
<tr><td><30</td><td rowspan="2">There is insufficient data and no dose adjustment recommendation can be made.</td><td>Moderate
Bilirubin 1.5-3 X ULN and any AST</td><td rowspan="2">No dose recommendation can be made due to insufficient data available</td></tr>
<tr><td></td><td></td><td>Severe
Bilirubin > 3 X ULN and any AST</td></tr>
<tr><td>CARBOplatin[b]</td><td colspan="2">See note below*</td><td colspan="2">No dose modification required</td></tr>
<tr><td>Etoposide[c]</td><td>CrCl (mL/min)</td><td>Dose</td><td>Hepatic impairment</td><td></td></tr>
<tr><td></td><td>>50</td><td>No dose adjustment is needed</td><td>Bilirubin < 50 µmol/L and
normal albumin and
normal renal function</td><td>No need for dose adjustment is expected</td></tr>
<tr><td></td><td>10-50</td><td>75% of the original dose, increase if tolerated</td><td rowspan="2">Bilirubin ≥ 50 µmol/L or
Decreased albumin levels</td><td rowspan="2">Consider 50% of the dose, increase if tolerated</td></tr>
<tr><td></td><td>Haemodialysis</td><td>Not dialysed, consider 75% of the original dose</td></tr>
<tr><td colspan="5">[a]Serplulimab (renal and hepatic – SmPC)
[b]CARBOplatin (renal and hepatic – NCCP standardisation)
[c]Etoposide (renal and hepatic – Giraud et al 2023)</td></tr>
</table>

[b]Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance (CrCl) values of <60mL/minute are at greater risk of developing myelosuppression
- If GFR between 20 to ≤ 30mL/minute, CARBOplatin should be administered with extreme caution
- If GFR ≤ 20mL/minute, 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 hours of drug administration

If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 5: Dose Modification of serplulimab for Adverse Events (CTCAE v5.0)

Immune-related adverse reactions	Severity	Treatment Modification*
Immune-related lung disease	Grade 2	Withhold until adverse reactions recover or improve to Grade 1
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold until adverse reactions recover or improve to Grade 1
	Grade 4 or recurrent Grade 3	Permanently discontinue
Hepatitis	Grade 2 with AST or ALT > 3 to 5 times ULN, or total bilirubin > 1.5 to 3 times ULN	Withhold until adverse reactions recover or improve to Grade 1
	Grade 3 or 4 with AST or ALT > 5 times ULN, or total bilirubin > 3 times ULN	Permanently discontinue
Nephritis and renal dysfunction	Grade 2 elevation of serum creatinine	Withhold until adverse reactions recover or improve to Grade 1
	Grade 3 or 4 elevation of serum creatinine	Permanently discontinue
Endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, Grade 2 or 3 hyperthyroidism, Grade 2 or 3 hypophysitis, Grade 2 adrenal insufficiency, Grade 3 hyperglycaemia or type 1 diabetes mellitus	Withhold until symptoms resolve and management with corticosteroids is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 hyperglycaemia	Permanently discontinue
Skin adverse reactions	Grade 3	Withhold until adverse reactions recover or improve to Grade 1
	Grade 4 Stevens Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue
Other immune-related adverse reactions	Grade 3 or 4 elevation of serum amylase or lipase Grade 2 or 3 pancreatitis Grade 2 myocarditis** Grade 2 or 3 other immune-mediated adverse reactions occurred for the first time Grade 3 decreased platelet count	Withhold until adverse reactions recover or improve to Grade 1

	(thrombocytopenia) or white blood cell count	
	Grade 4 pancreatitis or recurrent pancreatitis of any grade Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 4 other immune-related adverse reactions occurred for the first time Grade 4 or recurrent Grade 3 decreased platelet count (thrombocytopenia) or white blood cell count	Permanently discontinue
Infusion-related reactions	Grade 1	Patients with Grade 1 infusion-related reactions may continue administration under close monitoring.
	Grade 2	The rate of infusion should be reduced, or treatment should be interrupted in patients with Grade 2 infusion-related reactions. Antipyretic and antihistamines may be considered. Treatment with serplulimab may be resumed under close monitoring when Grade 2 infusion-related reactions are controlled.
	Grade 3 or 4	For Grade ≥ 3 infusion-related reactions, infusion should be stopped immediately, treatment should be permanently discontinued, and appropriate treatment should be given.

* Serplulimab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones
** The safety of retreatment with serplulimab in patients who experienced immune-related myocarditis is not clear.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

Serplulimab: Minimal (**Refer to local policy)**
CARBOplatin: High **(Refer to local policy)**
Etoposide: Low **(Refer to local policy)**

For information:
Within NCIS regimens, antiemetics have been standardised by the 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

PREMEDICATIONS:

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

OTHER SUPPORTIVE CARE:

- Women of childbearing potential should use effective contraception during treatment and for at least 6 months after the last dose of serplulimab.

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details
- **Serplulimab is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.**

DRUG INTERACTIONS:

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

REFERENCES:

1. Cheng Y, Han L, Wu L, et al. Effect of First-Line Serplulimab vs Placebo Added to Chemotherapy on Survival in Patients With Extensive-Stage Small Cell Lung Cancer: The ASTRUM-005 Randomized Clinical Trial. *JAMA.* 2022;328(12):1223–1232. doi:10.1001/jama.2022.16464
2. 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.
3. 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.
4. NCCN CARBOplatin dosing in adults. Available at: https://www.nccn.org/docs/default-source/clinical/order-templates/appendix_b.pdf?sfvrsn=6286822e_6.
5. Wright JG, Boddy AV, et al, Estimation of glomerular filtration rate in cancer patients. British Journal of Cancer 2001; 84(4):452-459
6. 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://pubmed.ncbi.nlm.nih.gov/37269847/
7. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. 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
8. Serplulimab (Hetronifly®) Summary of product characteristics. Accessed 03/07/2025. Available at: https://www.ema.europa.eu/en/documents/product-information/hetronifly-epar-product-information_en.pdf
9. CARBOplatin Summary of product characteristics. Accessed 07/07/2025. Available at: https://assets.hpra.ie/products/Human/28088/Licence_PA2059-032-001_02072024153224.pdf
10. Etoposide Summary of product characteristics. Accessed 07/07/2025. Available at: https://assets.hpra.ie/products/Human/27660/Licence_PA2315-201-001_13032024133422.pdf

Version	Date	Amendment	Approved By
1	08/08/2025		Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.