CISplatin (75mg/m^2) + Etoposide Therapy-21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Indicator
Small cell lung cancer (SCLC) extensive disease	C34	00280a	

If a reimbursement indicator (e.g. ODMS, CDS[i]) is not defined, the drug and its detailed indication have not gone through the formal reimbursement process as legislated for in the Health (Pricing and Supply of Medical Goods) Act 2013.

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.

CISplatin is administered on day 1 and etoposide is administered on three consecutive days (Days 1-3) of a 21day cycle for 4-6 cycles.

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

Admin Order	Day	Drug	Dose	Route	Diluent & Rate
1	1, 2 & 3	Etoposide	100mg/m^2	IV Infusion	1000ml 0.9% NaCl over 60mins
2	1	CISplatin	[a]75mg/m^2	IV Infusion	500-1000ml NaCl 0.9% over 2 hours (Pre and Post hydration therapy required)[b]

[a]The total dose of CISplatin may be fractionated and given over 3 days i.e. 25mg/m^2 on day 1

[b]Pre and post hydration therapy required for CISplatin
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) in 1000 mL sodium chloride 0.9% over 60 minutes.
2. Administer 200 mL of mannitol 20% over 15 minutes*(near the completion of the first bag of hydration fluids) (mannitol should be administered via a controlled infusion)

Administer CISplatin as described above
Post hydration: Administer 1000ml 0.9% NaCl over 60mins

*Mannitol 10% may be used as per institutional policy; there is much variation in the use of mannitol and although there is no conclusive evidence that mannitol should be used.

In cases of CISplatin toxicity or poorly functioning patients or age > 75 CARBOplatin AUC 5 **(Dose = AUC x (GFR* +25))** administered on Day 1 only may be substituted.

ELIGIBILTY:

- Indications as above
- ECOG status 0-3
- Life expectancy > 3 months

EXCLUSIONS:

- Hypersensitivity to etoposide, CISplatin or any of the excipients.
- CISplatin
  - Pre existing neuropathies ≥ grade 2
  - Creatinine clearance < 60 mL/min
  - Significant hearing impairment/tinnitus
- Severe liver impairment (etoposide)
- Pregnancy
- Breast Feeding

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

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

Regular tests:

- Blood, 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 1: Dose modification of ETOPOSIDE for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose Etoposide
≥ 1.5	**and**	≥ 100	100%
1-1.49	**or**	75-99	75%
< 1	**or**	< 75	DELAY

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

Drug	Renal impairment		Hepatic Impairment			
Etoposide	**Cr Cl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST (Units/L)**	**Dose Etoposide**
	>50	100%				
	15-50	75%	26-51	or	60-180	*50%
	Subsequent dosing should be based on patient tolerance and clinical effect. Data are not available in patients with CrCl < 15ml/min and further dose reductions should be considered in these patients.		>51	or	>180	Clinical decision
CISplatin	**GFR (ml/min)**	**Dose of CISplatin**	**No dose reduction necessary**			
	≥ 60	100%				
	45-59	75%				
	<45	Consider CARBOplatin/Clinical decision				

Table 3: Dose modification schedule based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Grade ≥ 2 peripheral neuropathy		Substitute CARBOplatin AUC 5 or 50% reduction of CISplatin dose after recovery to grade ≤ 1; 100% dose of etoposide.
Grade 3 (Other than mucositis or alopecia)		Delay until recovery to Grade 1. Then reduce dose of CISplatin and etoposide to 75%.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

PREMEDICATIONS:

Hydration prior and post CISplatin administration **(Reference local policy or see recommendations above).**

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. Avoid aminoglycoside antibiotics.
- **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.
- **Hypersensitivity:** Hypersensitivity reactions have been reported with etoposide and CISplatin. Monitor infusion of etoposide for the first 15 minutes for signs of hypotension.

DRUG INTERACTIONS:

- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Concomitant CISplatin therapy is associated with reduced total body clearance of etoposide.
- 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

ATC CODE:

CISplatin	L01XA01
Etoposide	L01CB01

REFERENCES:

1. Evans WK, Shepherd FA, Feld R, et al. VP-16 and CISplatin as first-line therapy for small-cell lung cancer. J Clin Oncol 1985; 3(11):1471-7.
2. Pujol JL, Carestia L, Daures JP. Is there a case for CISplatin in the treatment of small-cell lung cancer? A meta- analysis of randomized trials of a CISplatin-containing regimen versus a regimen without this alkylating agent. Br J Cancer 2000 Jul;83(1):8-15.
3. CISplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Accessed July 2017. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0749-119-002_06062013115044.pdf
4. Etoposide 20 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Accessed July 2017 Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1809-020-001_07102015115038.pdf

Version	Date	Amendment	Approved By
1	10/09/2015		Dr Maccon Keane
2	xx/xx/2017	Updated title and dosing in renal impairment, applied new NCCP regimen template	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] 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/