CISplatin (75mg/m^2) + Etoposide (100mg/m^2) + Radiotherapy (RT) - 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Small cell lung cancer (SCLC) limited disease	C34	00279a	Hospital
Small cell cancer of the cervix and other sites[i]	C53	00279b	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.

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

Usual plan is for radiotherapy to start with the first cycle of chemotherapy, although radiotherapy may be started with later cycles dependent on clinical circumstances.

Regimen may be administered every 28 days at discretion of prescribing consultant.

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

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

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 2 & 3	Etoposide	100mg/m^2	IV Infusion*	1000ml 0.9% NaCl over 1 hour	Every 21 days for 4 cycles
2	1	CISplatin[a, b]	[c]75mg/m^2	IV Infusion	1000ml 0.9% NaCl over 2 hours	Every 21 days for 4 cycles

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

- The administration of etoposide in 1000ml 0.9% NaCl over 1 hour as detailed above may be considered as pre-hydration for CISplatin
- Administer CISplatin as described above

Post hydration:

- Administer 10mmol magnesium sulphate ($MgSO_4$) and 20mmol potassium chloride (KCl) in 1000 ml 0.9% NaCl over 2 hours

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.)

[b]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.

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

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

ALTERNATE TREATMENT SCHEDULE:

CISplatin (75mg/m^2) + 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.

CISplatin 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 cycles according to the table below.

Usual plan is for radiotherapy to start with the first cycle of chemotherapy, although radiotherapy may be started with later cycles dependent on clinical circumstances.

Regimen may be administered every 28 days at discretion of prescribing consultant.

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

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Etoposide	100mg/m^2	IV Infusion[a]	1000ml 0.9% NaCl over 1 hour	Every 21 days for 4 cycles
2	1	CISplatin[b, c]	[d]75mg/m^2	IV Infusion	1000ml 0.9% NaCl over 2 hours	Every 21 days for 4 cycles
1	2, 3	Etoposide[e]	100mg/m^2 twice daily	PO		Every 21 days for 4 cycles

[a] If at the discretion of the treating consultant, etoposide is given orally on day 1, please ensure pre-hydration is given prior to CISplatin administration

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

- The administration of etoposide in 1000ml 0.9% NaCl over 1 hour as detailed above may be considered as pre-hydration for CISplatin
- Administer CISplatin as described above

Post hydration:

- Administer 10mmol magnesium sulphate ($MgSO_4$) and 20mmol potassium chloride (KCl) in 1000 ml 0.9% NaCl over 2 hours.

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.

[c]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.

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

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

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Suitable candidate for radiation

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 3: Dose modification of etoposide and CISplatin for haematological toxicity

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

Renal and Hepatic Impairment:

Table 4: Dose modification in renal and hepatic impairment

Drug	Renal impairment		Hepatic Impairment			
Etoposide	**CrCl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**			**Dose**
	>50	100%	<50	and	Normal albumin and renal function	No need for dose adjustment is expected
	10-50	75% of the original dose, increase if tolerated	≥50	or	Decreased albumin levels	Consider 50% of dose, increase if tolerated
	Haemodialysis	Not dialysed, consider 75% of original dose				
CISplatin	**CrCl (ml/min)**	**Dose**	No need for dose adjustment is expected			
	≥60	100%				
	50-59	75% of the original dose.				
	40-49	50% of the original dose.				
	<40	Not recommended				
	Haemodialysis	50% of the original dose may be considered				

Non-Haematological Toxicity:

Table 5: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Grade ≥ 2 peripheral neuropathy	Substitute cisplatin for 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 **(Refer to local policy).**
Etoposide: Low **(Refer to local policy).**

PREMEDICATIONS:
Hydration prior and post CISplatin administration **(Refer to 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.
- **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

REFERENCES:

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Version	Date	Amendment	Approved By
1	10/09/2015		Dr Maccon Keane
2	20/09/2017	Updated title and dosing in renal impairment, applied new NCCP regimen template	Prof Maccon Keane
3	09/01/2019	Updated CISplatin hydration protocol	Prof Maccon Keane
4	04/09/2019	Reviewed. Update of etoposide renal dosing	Prof Maccon Keane
5	24/06/2021	Reviewed. Updated CISplatin hydration protocol.	Prof Maccon Keane
6	24/03/2023	Alternate treatment schedule included. Updated dose modification for haematological toxicities	Prof Maccon Keane
7	27/09/2023	New indications added (00279b). Updated recommendations for dose modifications in renal and hepatic impairment.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of CISplatin and etoposide in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating

any relevant information to the patient and also ensuring that the unlicensed or “off label” indication has been acknowledged by the hospital’s Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.