Gemcitabine (1250mg/m^2) and CISplatin (80mg/m^2) Therapy- 21 day[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Treatment of locally advanced nasopharyngeal cancer	C11	00517a	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.

Gemcitabine is administered on day 1 and day 8 and CISplatin is administered on day 1 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 the chemotherapy is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1 and 8	Gemcitabine	1250mg/m^2	IV infusion	250ml NaCl 0.9% over 30mins	Every 21 days
2	1	*CISplatin	80mg/m^2	IV infusion	1000ml NaCl 0.9% over 120mins	Every 21 days

***Pre and post hydration therapy required for CISplatin**

See local hospital policy recommendations.

Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 20mmol/L if indicated) in 1000mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above

Post hydration: Administer 1000 ml 0.9% NaCl over 60mins

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 (4,5).

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate marrow reserve (ANC > 1.5 x 10^9/L, platelets > 100x10^9/L)

EXCLUSIONS:

- Hypersensitivity to Gemcitabine, CISplatin or any of the excipients
- CISplatin
  - Pre existing neuropathies ≥ grade 2
  - Creatinine clearance < 60 mL/min
  - Significant hearing impairment/tinnitus
- Breast Feeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Audiometry and creatinine clearance as clinically indicated

Regular tests:

- Day 1: FBC, renal and liver profile
- Day 8: FBC, creatinine

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:

Prior to commencing a new treatment cycle (i.e day 1), ANC must be ≥1 x 10^9/L and platelets ≥ 100 x 10^9/L.

Table 1: Dose modifications for gemcitabine within a cycle (i.e day 8)

ANC (x 10^9 /L)		Platelet count (x 10^9 /L)		Other toxicity	Recommended dose of Gemcitabine
≥1	and	≥ 100			100 %
0.5- 1	or	50-100			75%
< 0.5	or	<50			Omit. Do not restart treatment until ANC ≥ 0.5 and platelets ≥ 50
ANC < 0.5 for ≥ 5 days **or** ANC < 0.1 for ≥ 3 days **or** Any incidence of febrile neutropenia	**or**	< 25	**or**	cycle delay of >1 week due to any toxicity	Reduce dose to 75% of the original cycle initiation dose for all subsequent cycles.

Renal and Hepatic Impairment:

Table 2: Dose modification of CISplatin and Gemcitabine in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
	Cr Cl (ml/min	Dose	No dose reductions necessary
CISplatin	>60	100%	
	45-59	75%	
	<45	Consider CARBOplatin-Clinical decision	
Gemcitabine	≥30	100%	AST elevations do not seem to cause dose limiting toxicities. If bilirubin ≥ 27 micromol/L, initiate treatment with dose of 800 mg/m^2.
	<30	Consider dose reduction clinical decision	

Management of adverse events:

Table 3: Dose Modification of Gemcitabine and CISplatin for Adverse Events

Adverse reactions	Recommended dose modification
Grade ≥ 3 Non-haematological toxicity (except nausea/vomiting)	Therapy with Gemcitabine and CISplatin should be withheld (until toxicity has resolved to grade ≤ 1) and may be resumed with dose reduction at discretion of prescribing consultant.
Grade ≥ 2 peripheral neuropathy	Substitute CARBOplatin AUC 5 or 50% reduction of CISplatin dose after recovery to grade ≤ 1. 100% dose of Gemcitabine
Grade ≥ 2 pneumonitis	Discontinue gemcitabine

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

PREMEDICATIONS:

Pre and Post Hydration therapy required for CISplatin administration **(Reference local policy or see recommendations above).**

OTHER SUPPORTIVE CARE:

Patient should be encouraged to drink large quantities of liquids for 24 hours after the CISplatin infusion to ensure adequate urine secretion.

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. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Irreversible renal failure associated with hemolytic uremic

syndrome may occur (rare) with Gemcitabine. Use caution with pre-existing renal dysfunction.

- **Pulmonary Toxicity**: Acute shortness of breath may occur with gemcitabine. Discontinue treatment if drug-induced pneumonitis is suspected.
- **Cardiovascular:** Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.

DRUG INTERACTIONS:

- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Gemcitabine	L01BC05
CISplatin	L01XA01

REFERENCES:

1 Yau TK, Lee AW, Wong DH, Yeung RM, et al. Induction chemotherapy with cisplatin and gemcitabine followed by accelerated radiotherapy and concurrent cisplatin in patients with stage IV(A-B) nasopharyngeal carcinoma. Head Neck 2006;28(10):880-7.

2 BCCA Protocol Summary for Induction Treatment of Locally Advanced Nasopharyngeal Cancer with CISplatin and Gemcitabine. Using Gemcitabine Protocol code HNNLAPG revised November 2012

3 EVIQ Protocol Summary for Nephrotoxicity associated with cisplatin- Using Protocol code 184 revised June 2016.

4 Portilla D et al. CISplatin nephrotoxicity. UptoDate Accessed Sept 2018 https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150

5 Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf

6 Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network. Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf

7 Cisplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Accessed October 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-081-001_13022020153905.pdf

8 Gemcitabine 100 mg/ml Concentrate for Solution for Infusion Summary of Product CharacteristicsOctober 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-092-004_25062020164320.pdf

Version	Date	Amendment	Approved By
1	07/11/2018		Prof Maccon Keane
2	23/10/2020	Reviewed	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This indication is outside the licensed indications for Gemcitabine in Ireland. Patients should be informed of the unlicensed nature of this indication 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 aware of their responsibility in communicating any relevant information to the patient and also in 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.