CISplatin and 5-Fluorouracil Therapy-28 day cycle

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Locally advanced or metastatic head and neck cancer	C76	00314a	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 and 5-Fluorouracil are administered on days 1-4 of a **28-day** cycle until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered on Day 1.

Admin. Order	Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1	1-4	[a]CISplatin	25mg/m^2	IV infusion	1000mL 0.9% NaCl over 2 hours	Every 28 days
2	1-4	[b]5-Fluorouracil	1000mg/m^2/ day	IV infusion	1000mL 0.9% NaCl over 22 hours	Every 28 days
[a]Pre hydration therapy required for CISplatin See local hospital policy recommendations. Suggested pre-hydration for CISplatin therapy: 1. Administer 10mmol magnesium sulphate ($MgSO_4$) (+/-KCl 20mmol/L if indicated) in 1000 mL NaCl 0.9% over 60 minutes. Administer CISplatin as described above						
[b]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency						

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Adequate organ function; ANC > 1.5 x10^9 cells/L, platelets 100 x10^9/L serum creatinine≤ 1.5 x ULN, transaminases ≤5 x ULN, bilirubin ≤1.5 x ULN

EXCLUSIONS:

- Hypersensitivity to CISplatin, 5-Fluorouracil or any of the excipients
- Pregnancy
- Lactation
- Pre-existing neuropathies ≥ grade 2
- Severe liver impairment
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Significant hearing impairment/tinnitus
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, Renal and liver profile
- ECG (if patient has compromised cardiac function).
- Audiology and creatinine clearance if clinically indicated
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested
    - In patients with moderate or severe renal impairment, blood uracil levels used for dihydropyrimidine dehydrogenase (DPD) phenotyping should be interpreted with caution, as impaired kidney function can lead to increased uracil blood levels. Consequently, there is an increased risk for incorrect diagnosis of DPD deficiency, which may result in under dosing of 5-Fluorouracil or other fluoropyrimidines, leading to reduced treatment efficacy. Genotype testing for DPD deficiency should be considered for patients with renal impairment.

Regular tests:

- FBC, Renal and liver profile before 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:

- Consider a reduced starting dose in patients with identified partial DPD deficiency
    - Initial dose reduction may impact the efficacy of treatment
    - In the absence of serious toxicity, subsequent doses may be increased with careful monitoring
- Any dose modification should be discussed with a Consultant

Haematological:

Table 1: Dose modification for haematological toxicity

ANC (x 10^9/L) (on day of chemotherapy)		Platelets (x 10^9/L) (at any stage during cycle)	Dose of 5-Fluorouracil
1 -1.5	or	75-100	750mg/m^2/day x 4 days
<1	or	<75	375mg/m^2/day x 4 days

Renal and Hepatic Impairment:

Table 2: Dose modification for renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
CISplatin	**GFR (mL/min)**	**Dose**	No dose reduction necessary			
	≥60	100%				
	45-59	75%				
	<45	Clinical decision. Consider using CARBOplatin				
5-Fluorouracil	Consider dose reduction in severe renal impairment only		**Bilirubin**		**AST**	**Dose**
			<85		<180	100%
			>85	or	>180	Contra-indicated
			Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2. Increase dose if no toxicity.			

Non-haematological toxicity

Table 3: Dose modification schedule for CISplatin based on adverse events

Adverse reaction	Recommended dose modification
Grade ≥ 2 peripheral neuropathy	Omit CISplatin and consider substituting CISplatin with CARBOplatin

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: High (**Refer to local policy).**

PREMEDICATIONS: Hydration prior 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.
- **Renal toxicity:** Renal toxicity is common with CISplatin. Encourage oral hydration.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.
- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with 5-Fluorouracil, should be carefully monitored during therapy.
- **DPD deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent

doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.

- **Hand-foot syndrome (HFS),** also known as palmar-plantar erythrodysaesthesia (PPE) has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-Fluorouracil.

DRUG INTERACTIONS:

- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary, monitor renal function closely.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of 5-Fluorouracil regimes.
- Concurrent administration of 5-Fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPD activity.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: A Southwest Oncology Study. J Clin Oncol, 1992; 10: 1245-1251
2. BCCA Protocol Summary for Advanced Nasopharyngeal Cancer of the Head and Neck using Platinum and Fluorouracil HNNAVFUP Revised October 2013
3. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
4. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting V2 2019. 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
6. HPRA Direct Healthcare Professional Communication. 5-Fluorouracil (i.v.), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity. Accessed Aug 2020 Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-from-marketing-authorisation-holders-of-products-containing-5-fluorouracil-(i-v-)-capecitabine-and-tegafur-as-approved-by-the-hpra.pdf?sfvrsn=0
7. Cisplatin 1mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Accessed May 2020. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-081-001_13022020153905.pdf
8. Fluorouracil 50mg/ml Solution for injection or Infusion Summary of Product Characteristics Accessed May 2020. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-091-001_10052019144741.pdf

Version	Date	Amendment	Approved By
1	03/05/2016		Prof Maccon Keane
2	02/05/2018	Applied new NCCP regimen template. Updated treatment table, revised CISplatin hydration regimen recommendations and standardised dosing in renal and hepatic impairment.	Prof Maccon Keane
3	13/05/2020	Exclusion criteria updated	Prof Maccon Keane
4	24/08/2020	Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020 Updated Adverse events regarding palmar-plantar erythrodysaesthesia	Prof Maccon Keane
4a	22/11/2023	Formatting changes and grammatical corrections.	NCCP
4b	24/02/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.