CISplatin 75mg/m^2 and 5-Fluorouracil Chemoradiation Therapy-Herskovic Regimen

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Locally advanced squamous or adenocarcinoma of the oesophagus not suitable for surgery	C15	00460a	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.

Chemotherapy is administered on weeks 1, 5, 8 and 11* with CISplatin being administered on Day 1 and 5-Fluorouracil being administered by continuous infusion on Days 1-4.
Radiotherapy is administered concurrently with chemotherapy* during weeks 1-5.
*unless disease progression or unacceptable toxicity develops.
Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Order of Admin	Week	Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Comment
1	1, 5	1	[a]CISplatin	75mg/m^2	IV infusion	1000ml NaCl 0.9% over 2 hours	Concurrently with radiotherapy (week 1-5)
2	1, 5	1-4	[b]5-Fluorouracil	1000mg/m^2/day	Continuous IV infusion over 4 days	Infusor pump	Concurrently with radiotherapy (week 1-5)
1	8, 11	1	[a]CISplatin	75mg/m^2	IV infusion	1000ml NaCl 0.9% over 2 hours	
2	8, 11	1-4	5-Fluorouracil	1000mg/m^2/day	Continuous IV infusion over 4 days	Infusor pump	

[a,] **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 1000 mL 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 (3, 4).

[b] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency

ELIGIBILITY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to CISplatin, 5-Fluorouracil or any of the excipients
- Pregnancy
- Breast Feeding
- Creatinine Clearance<60ml/min
- 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
- Audiometry and creatinine clearance as clinically indicated
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- FBC, renal and liver profile

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 Modification
≥1	and	≥100	100% Dose
0.5 -0.99	or	50-99	Delay treatment until recovery
<0.5	or	<50	Delay treatment until recovery and consider reducing CISplatin and 5-Fluorouracil by 25% for subsequent cycles
Febrile neutropenia			

Renal and Hepatic Impairment:

Table 2: Dose Modification for in Renal and Hepatic Impairment

Drug	Renal Impairment		Hepatic Impairment			
CISplatin	**CrCl (ml/min)**	**Dose**	No dose reductions necessary			
	>60	100%				
	45-59	75%				
	<45	Consider CARBOplatin-Clinical decision				
5-Fluorouracil	Consider dose reduction in severe renal impairment only		**Bilirubin (micromol/L)**		**AST**	**Dose**
			<85		<180	100%
			>85	or	>180	Contraindicated
			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.			

Table 3: Dose Modifications for Adverse Events

Adverse reactions	Recommended dose modification
Grade ≥ 3 Diarrhoea or Stomatitis	Delay treatment until toxicity has resolved to grade ≤ 1 and then treatment may be resumed with a 25% reduction in the dose of 5-Fluorouracil.
Grade ≥ 2 peripheral neuropathy	Omit CISplatin

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CISplatin High (**Refer to local policy)**
5-Fluorouracil 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

- **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
- **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:

- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- 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
- 5-Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5- Fluorouracil -metabolising enzyme DPD.
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPDactivity.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CISplatin	-	L01XA01
5-Fluorouracil	-	L01BC02

REFERENCES:

1. Herskovic A, Martz K, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med. 1992;326(24):1593.
2. al-Sarraf M, Martz K et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol. 1997;15(1):277.
3. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3 https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-prevention/184-nephrotoxicity-associated-with-CISplatin
4. Portilla D et al. CISplatin nephrotoxicity. UptoDate Accessed Oct 2017 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.
6. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network.
7. 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
8. 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
9. Cisplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Accessed Nov 2017. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0749-119-002_06062013115044.pdf
10. Fluorouracil 25 mg/ml Solution for Injection or Infusion SmPC HPRA.Updated 10/10/2019. Accessed Jan 2020. Available at; https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-223-001_10102019120038.pdf

Version	Date	Amendment	Approved By
1	16/02/2018		Prof Maccon Keane
2	26/02/2020	Reviewed. Update of exclusions. Standardization of 5-fluorouracil hepatic dose modifications. Update of drug interactions.	Prof Maccon Keane
3	1/9/2020	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
3a	23/11/2023	Formatting changes and grammatical corrections.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.