

## CARBOplatin 70mg/m<sup>2</sup> and 5-Fluorouracil 600mg/m<sup>2</sup> with Radiotherapy

### INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Locally Advanced Squamous Cell Carcinoma of the Head and Neck	C76	00589a	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.

CARBOplatin and 5-Fluorouracil are administered on Day 1-4 every 21 days for three cycles.

Chemotherapy is only to be administered if concurrent with radiotherapy.

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1-4	CARBOplatin	70mg/m <sup>2</sup>	IV Infusion	250mL glucose 5% over 30 mins	Every 21 days for three cycles
2	1-4	5-Fluorouracil <sup>a</sup>	600mg/m <sup>2</sup> /day	Continuous IV infusion over 4 days (96 hours)	Infusor pump	Every 21 days for three cycles

<sup>a</sup>See dose modifications section for patients with identified partial Dihydropyrimidine dehydrogenase (DPD) deficiency

### ELIGIBILITY:

- Indication as above
- Stage III or IV squamous cell carcinoma of the oropharynx without evidence of distant metastases
- ECOG 0-2

### USE WITH CAUTION:

- Pre-existing motor or sensory neuropathy > grade 2

### EXCLUSIONS:

- Hypersensitivity to CARBOplatin\*, 5-Fluorouracil or any of the excipients
- Neutrophil count <1.5x10<sup>9</sup>/L
- Platelet count <100x10<sup>9</sup>/L
- Renal insufficiency with creatinine >120 micromol/L or Creatinine clearance ≤50 mL/min
- Bilirubin >1.5xULN

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- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency  
\*If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision

## PRESCRIPTIVE AUTHORITY:

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

## TESTS:

### Baseline tests:

- FBC, renal and liver profile
- Audiology and creatinine clearance if clinically indicated
- Dihydropyrimidine dehydrogenase (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 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:

- 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 of CARBOplatin and 5-Fluorouracil in haematological toxicity**

ANC ( $\times 10^9$ /L)		Platelets ( $\times 10^9$ /L)	Dose
$\geq 1.5$	and	$\geq 100$	100%
1.0-1.5	or	75-99	75%
$< 1.0$	or	$< 75$	Delay one week

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## Renal and Hepatic Impairment:

**Table 2: Dose modification of CARBOplatin and 5-Fluorouracil in renal and hepatic impairment**

Drug	Renal Impairment		Hepatic Impairment			
	Creatinine (micromol/L)	Dose	Bilirubin (micromol/L)		AST	Dose
CARBOplatin	≤120	100%	No need for dose adjustment is expected.			
	>120	Delay one week.				
5-Fluorouracil	Renal impairment: no need for dose adjustment is expected		<85		<180	100%
			>85	or	>180	Contraindicated
	Haemodialysis: no need for dose adjustment is expected		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.			

## Management of adverse events:

**Table 3: Dose Modification for Adverse Events**

Adverse reactions	Recommended dose modification
<b>Dysphagia or stomatitis:</b>	
Grade 0-2	100%
Grade 3	Delay until improvement and proceed at 75-100%
Grade 4	Discontinue
<b>Weight loss from baseline:</b>	
≤10%	100%
>10%	75% if hyperalimentation instituted, otherwise discontinue
<b>Palmar-plantar erythrodysesthesia:</b>	
Grade 0-2	100%
Grade 3	75%

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

CARBOplatin Moderate (**Refer to local policy**).

5-Fluorouracil Low (**Refer to local policy**).

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**PREMEDICATIONS:** No specific recommendations

**OTHER SUPPORTIVE CARE:** Anti-diarrhoeal treatment (Refer to local policy).

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

### CARBOplatin

- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as paraesthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with cisplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.

### 5-Fluorouracil

- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with 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.
- **Dihydropyrimidine dehydrogenase (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 fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.
- **Hand-foot syndrome (HFS):** HFS, also known as palmar-plantar erythrodysesthesia (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 CARBOplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDs) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDs). If necessary perform regular audiometric testing.
- Marked elevations of prothrombin time and INR have been reported in patients stabilised on warfarin therapy following initiation of fluorouracil regimens.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin.

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- 5-Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-Fluorouracil -metabolising enzyme dihydropyrimidine dehydrogenase (DPD).
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	18/9/2020		Prof Maccon Keane
2	22/10/2021	Reviewed. Updated drug interactions.	Prof Maccon Keane
3	14/12/2023	Updated baseline tests and exclusions sections. Updated renal and hepatic dose modifications table. Update to other supportive care section.	Prof Maccon Keane

Comments and feedback welcome at [oncologydrugs@cancercontrol.ie](mailto:oncologydrugs@cancercontrol.ie).

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