# CARBOplatin 70mg/m$^2$ and 5-Fluorouracil 600mg/m$^2$ with Radiotherapy

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | HSE approved reimbursement status |
|---|---|---|---|
| Locally Advanced Squamous Cell Carcinoma of the Head and Neck | C76 | 00589a | N/A |

*This applies to post 2012 indications only

## 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 anaphylasis 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$^2$ | IV Infusion | 250mL glucose 5% over 30 minutes | Every 21 days for three cycles |
| 2 | 1-4 | 5-Fluorouracil[a] | 600mg/m$^2$/day | Continuous IV infusion over 4 days (96 hours) | Infusor pump | Every 21 days for three cycles |
| [a]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$^9$/L
- Platelet count <100x10$^9$/L
- Renal insufficiency with creatinine >120 micromol/L or Creatinine clearance ≤50 mL/min

- Bilirubin >1.5xULN
- 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
    - 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 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 (x10$^9$/L) | | Platelets (x10$^9$/L) | Dose |
|---|---|---|---|
| ≥1.5 | and | ≥100 | 100% |
| 1.0-1.5 | or | 75-99 | 75% |
| <1.0 | or | <75 | Delay one week |

## Renal and Hepatic Impairment:

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

<table>
<tr><th></th><th colspan="2">Renal Impairment</th><th colspan="4">Hepatic Impairment</th></tr>
<tr><td rowspan="3">CARBOplatin</td><td>Creatinine (micromol/L)</td><td>Dose</td><td colspan="4" rowspan="3">No need for dose adjustment is expected.</td></tr>
<tr><td>≤120</td><td>100%</td></tr>
<tr><td>>120</td><td>Delay one week.</td></tr>
<tr><td rowspan="4">5-Fluorouracil</td><td colspan="2" rowspan="4">Renal impairment: no need for dose adjustment is expected<br><br>Haemodialysis: no need for dose adjustment is expected</td><td>Bilirubin (micromol/L)</td><td></td><td>AST</td><td>Dose</td></tr>
<tr><td><85</td><td></td><td><180</td><td>100%</td></tr>
<tr><td>>85</td><td>or</td><td>>180</td><td>Contraindicated</td></tr>
<tr><td colspan="4">Clinical decision.<br>Moderate hepatic impairment; reduce initial dose by 1/3.<br>Severe hepatic impairment, reduce initial dose by 1/2.<br>Increase dose if no toxicity.</td></tr>
</table>

## Management of adverse events:

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

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

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

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

**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 parasthesia, 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 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 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 regimes.
- Concurrent administration of 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 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.

## REFERENCES:


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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. V5 2023. 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. CARBOplatin Summary of Product Characteristics . Accessed July 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-032-001_10112019092721.pdf
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| Version | Date | Amendment | Approved By |
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| 1 | 18/09/2020 | | 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 |
| 3a | 13/03/2025 | Additional wording added to baseline testing section. | NCCP |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.