# Cetuximab (weekly), CARBOplatin AUC 5 and 5-Fluorouracil 1000mg/m$^2$/day Therapy - 21 day cycle

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | *Reimbursement Status |
|---|---|---|---|
| Locally advanced or metastatic squamous cell head and neck cancer in patients where CISplatin is contraindicated or not tolerated. | C76 | 00418a | Hospital |

*If the reimbursement status is not defined[i], the indication has yet to be assessed through the formal reimbursement process.*

## 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.*

Cetuximab is administered once weekly on days 1, 8 and 15, CARBOplatin is administered on Day 1 and 5-FU is administered on days 1-4 of a 21 day cycle for up to 6 cycles until disease progression or unacceptable toxicity develops.
Chemotherapy must not be administered earlier than 1 hour after the end of the cetuximab infusion.
Availability of resuscitation equipment MUST be ensured while administering cetuximab.

| Admin. Order | Day | Drug | Dose | Route and Method of Administration | Diluent & Rate | Cycle |
|---|---|---|---|---|---|---|
| 1 | 1 | Cetuximab | 400mg/m$^2$ | [a]IV Observe post infusion | [b]Over 120mins | 1 |
| | 8,15 | Cetuximab | 250mg/m$^2$ | [a]IV Observe post infusion | Over 60mins | 1 |
| 1 | 1,8,15 | Cetuximab | 250mg/m$^2$ | IV | Over 60mins | 2 onwards |
| 2 | 1 | CARBOplatin | AUC 5 | IV infusion | 500ml glucose 5% over 2 hours | 1-6 |
| 3 | 1-4 | [c]5-FU | 1000mg/m$^2$ | IV infusion | 1000ml 0.9% NaCl over 16-22 hours | 1-6 |

[a]Obtain vital signs pre-infusion, at 1 hr and post-infusion. 1hr observation period following end of 1st and 2nd infusion. If no infusion reaction occurs for 2 consecutive doses, then may discontinue observation period and vital signs

[b]The initial dose should be given slowly and speed of infusion must not exceed 5 mg/min. The recommended infusion period is 120 minutes.
For the subsequent weekly doses, the recommended infusion period is 60 minutes. The maximum infusion rate must not exceed 10 mg/min.
May be administered diluted in 0.9% NaCl or undiluted.
Flush the line with 0.9% NaCl at the end of the cetuximab infusion.

[c]Alternatively 5-FU may be administered at 2000mg/m$^2$ over 48 hours on day 1 and day 2 and then repeated on day 3 and day 4 for a total dose of 4000mg/m$^2$ over 96 hours

**CARBOplatin dose:**

The dose in mg of CARBOplatin to be administered is calculated as follows:

**(mg) = target AUC (mg/ml x min) x (GFR ml/min +25)**

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible
- **Estimation of GFR (eGFR)** can be done by using the Wright formula or using the Cockroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese and anorexic patients the formulae may not give accurate results and measured GFR is recommended. Where obesity or overweight is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight for Cockroft and Gault may be considered (3).

**WRIGHT FORMULA**

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (µmol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (µmol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

**COCKCROFT-GAULT FORMULA**

$$\text{GFR (ml/min)} = \frac{S \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

## ELIGIBILTY:

- Indication as above
- ECOG status 0-2
- Adequate organ function
- ANC > 1.5 x$10^9$ cells/L, platelets 100 x$10^9$/L, serum creatinine≤ 1.5 x ULN, transaminases ≤5 xULN, bilirubin ≤1.5 x ULN

## EXCLUSIONS:

- Hypersensitivity to cetuximab, *CARBOplatin, 5-FU or any of the excipients
- Lactation
- Fluorouracil (5-FU) should not be given to patients who are known to be homozygotic for dihydropyrimidine dehydrogenase (DPD) or in patients with a known complete absence of DPD activity

## PRESCRIPTIVE AUTHORITY:

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

## TESTS:

**Baseline tests:**

- FBC, renal and hepatic profile (including magnesium)
- ECG (if patient has compromised cardiac function).
- Audiology if clinically indicated
- Complete medical history specifically asking about any previous infusion related reactions (IRR) to another antibody, allergy to red meat or tick bites, or any results of tests for IgE antibodies against cetuximab.

**Regular tests:**

- FBC, renal and hepatic profile (including magnesium) before each cycle
- Post treatment: monthly electrolytes, magnesium, calcium for 2 months after last cetuximab treatment

**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:**

**Table 1: Dose Modification for Haematologiocal toxicity**

| **ANC (x $10^9$/L) ( on day of chemotherapy)** | | **Platelets (x $10^9$/L) ( at any stage during cycle)** | **Dose Modification** |
|---|---|---|---|
| ≥1.5 | and | ≥100 | 100% Dose |
| 0.5 -1.5 | or | 50-99 | Delay treatment until recovery |
| <0.5 | or | <50 | Delay treatment until recovery and consider reducing CARBOplatin and 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 | | | |
|---|---|---|---|---|---|
| Cetuximab | Clinical decision-unlikely to require a reduction | Unlikely to require a dose reduction | | | |
| CARBOplatin | See note below* | No dose modification required | | | |
| 5-Fluorouracil | Consider dose reduction in severe renal impairment only | **Bilirubin (micromol/L)** | | **AST** | **Dose** |
| | | <85 | | <180 | 100% |
| | | >85 | or | >180 | Contraindicated |
| | | 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 | | | |

*Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of < 60ml/min are at greater risk to develop myelosuppression.
- In case of GFR ≤ 20ml/min CARBOplatin should not be administered at all.
- If Cockroft & Gault or Wright formula are used, the dose should be adjusted per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to remeasuring the GFR or to recalculating using Cockroft &Gault or Wright formulae taking care this does result in a dose reduction

## Non-haematological toxicity

**Table 3: Dose modification schedule for Cetuximab based on adverse events**

| Adverse reaction | Discontinue | Recommended dose modification |
|---|---|---|
| **Infusion Reaction**<br>Grade 1<br><br>Grade 2<br><br><br>Grade 3 and 4 | | <br>Continue slow infusion under close supervision.<br><br>Continue slow infusion and immediately administer treatment for symptoms.<br><br>Stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab |
| **Interstitial lung disease** | Discontinue | |
| **Skin reaction**<br>**Grade 1 or 2** | | No dosage adjustment required. See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions. |
| **Severe skin reaction**<br>**≥ grade 3***<br>First occurrence<br><br><br>Second occurrence<br><br><br>Third occurrence<br><br>Fourth occurrence | <br><br><br><br><br><br><br><br>Discontinue | <br><br>Hold cetuximab treatment for a maximum of 2 weeks.<br>Reinitate therapy only if reaction has resolved to grade 2 at 250mg/m$^2$<br>Hold cetuximab treatment for a maximum of 2 weeks.<br>Reinitate therapy only if reaction has resolved to grade 2 at 200mg/m$^2$<br>Hold cetuximab treatment for a maximum of 2 weeks. Reinitate therapy only if reaction has resolved to grade 2 at 150mg/m$^2$ |

*** See other supportive care section below**

## SUPPORTIVE CARE:

**EMETOGENIC POTENTIAL:**

- **Cetuximab** Low (**Refer to local policy**)
- **5-Fluorouracil** Low (**Refer to local policy**)
- **CARBOplatin (AUC ≥4)** High (**Refer to local policy**)

**PREMEDICATIONS:**
Patients must receive premedication with an antihistamine and a corticosteroid prior to cetuximab infusion. This premedication is recommended prior to all subsequent infusions. Patient should be educated about the possibility of delayed infusion-related symptoms.

**OTHER SUPPORTIVE CARE:**
See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions. **(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*
**Cetuximab**

- **Infusion-related reactions:**
  - The first dose should be administered slowly and the speed must not exceed 5 mg/min whilst all vital signs are closely monitored for at least two hours. If during the first infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the patient may have preformed IgE antibodies before a subsequent infusion is given.
  - If an IRR develops later during the infusion or at a subsequent infusion further management will depend on its severity (Ref Table 3)
  - In cases of mild or moderate infusion-related reaction, the infusion rate may be decreased and maintained at the lower rate in all subsequent infusions.
  - Severe infusion-related reactions may occur with symptoms usually occurring during the first infusion and up to 1 hour after the end of the infusion. They may occur several hours after or with subsequent infusions. Patients should be warned of the possibility of such a late onset and instructed to contact their physician if symptoms occur
  - Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment.
  - Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease.
- **Respiratory disorders:** Interstitial lung disease has been observed with EGFR inhibitors. Treatment should be withheld in the event of onset or worsening respiratory symptoms. If pneumonitis or lung infiltrates are confirmed, treatment should be discontinued**.**
- **Cardiovascular:** An increased frequency of severe and sometimes fatal cardiovascular events and treatment emergent deaths has been observed. When prescribing cetuximab, the cardiovascular and performance status of the patients and concomitant administration of cardiotoxic compounds such as fluoropyrimidines should be taken into account.
- **Skin reactions:** This is the main adverse reaction of cetuximab. Refer to local policy for skin care regime and to Table 3 under Dose Modifications for management of treatment if patient experiences skin reactions.

- **Electrolyte disturbances:** Hypomagnesaemia, hypokalaemia or hypocalcaemia may occur. Electrolyte repletion is recommended, as appropriate.
- **Neutropenia:** Increased risk of severe neutropenia in patients who receive cetuximab in combination with platinum-based chemotherapy, which may lead to subsequent infectious complications such as febrile neutropenia, pneumonia or sepsis.

**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 fluorouracil, should be carefully monitored during therapy.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** Rare, life-threatening toxicities such as stomatitis, mucositis, neutropenia, neurotoxicity and diarrhoea have been reported following administration of fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation prior to continuing with treatment.

## 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 stabilized on warfarin therapy following initiation of fluorouracil regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin
- Fluorouracil (5-FU) is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD).
- Current drug interaction databases should be consulted for more information.

## ATC CODE:

| | | |
|---|---|---|
| Cetuximab | - | L01XC06 |
| CARBOplatin | - | L01XA02 |
| 5-Fluorouracil | - | L01BC02 |

## REFERENCES:


1. Vermorken JB, Ricard MD, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27
2. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2012; 30 (13) 1553-1561.
3. Ekhart C, Rodenhuis S et al. Carboplatin dosing in overweight and obese patients with normal renal function, does weight matter? Cancer Chemother Pharmacol 2009;64:115-122.
4. Carboplatin Summary of Product Characteristics HPRA. Last updated: 05/04/2019. Accessed May 2019 Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-032-001_05042019122803.pdf
5. Erbitux® Summary of Product Characteristics EMA. Last updated: 25/03/2019 Accessed May 2019 Available at https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf
6. Fluorouracil 50 mg/ml Solution for Injection or Infusion SmPC HPRA. Last updated: 01/05/2019. Accessed May 2019. Available at; https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-091-001_01052019171125.pdf


| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 08/05/2017 | | Prof Maccon Keane |
| 2 | 16/05/2019 | Update of exclusion criteria, tests, adverse events, drug interactions and emetogenic potential. | Prof Maccon Keane |
| 3 | 09/10/2019 | Update of exclusion criteria | Prof Maccon Keane |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/